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<p>(21) International Application Number: PCT/CA90/00076</p> <p>(22) International Filing Date: 9 March 1990 (09.03.90)</p> <p>(30) Priority data: 321,926 10 March 1989 (10.03.89) US</p> <p>(71) Applicant: ENDORECHERCHE INC. [CA/CA]; 2989 de la Promenade Ste-Foy, Quebec, Quebec G1W 2J6 (CA).</p> <p>(72) Inventor: LABRIE, Fernand ; 2989 de la Promenade Ste-Foy, Quebec, Quebec G1W 2J6 (CA).</p>		<p>(74) Agent: HEWITT, Neville, S.; Marks &amp; Clerk, P.O. Box 957, Station B, Ottawa, Ontario K1P 5S7 (CA).</p> <p>(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: COMBINATION THERAPY FOR TREATMENT OF ESTROGEN SENSITIVE DISEASES</p> <p>(57) Abstract</p> <p>A method of treatment of breast and endometrial cancer in susceptible warm-blooded animals may include inhibition of ovarian hormonal secretion by surgical (ovariectomy) or chemical (use of an LHRH agonist, e.g. [D-Trp<sup>6</sup>, des-Gly-NH<sub>2</sub><sup>10</sup>]LHRH ethylamide or antagonist) as part of a combination therapy comprising administering an antiestrogen together with at least one compound selected from the group consisting of an androgen, a progestin, at least one inhibitor of sex steroid formation, especially 17<math>\beta</math>-hydroxysteroid dehydrogenase and aromatase activity, at least one inhibitor of prolactin secretion, one inhibitor of growth hormone secretion and one inhibitor of ACTH secretion. Pharmaceutical compositions useful for such treatment and pharmaceutical kits containing such compositions are disclosed.</p>		

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COMBINATION THERAPY FOR TREATMENT OF ESTROGEN SENSITIVE  
DISEASES

## BACKGROUND OF THE INVENTION

This invention relates to a method of treatment of breast and endometrial cancer in susceptible warm-blooded animals including humans and in particular to combination therapy involving administration of anti-estrogens in combination with other inhibitors of hormone production, inhibitors of hormone functions and/or in combination with other hormones.

Various investigators have been studying hormone-dependent breast and endometrial cancer. A known form of endocrine therapy in premenopausal women is castration most commonly performed by surgery or irradiation, two procedures giving irreversible castration. Recently, a reversible form of castration has been achieved by utilizing Luteinizing Hormone Releasing Hormone agonists ("LHRH agonists") which, following inhibition of secretion of bioactive Luteinizing Hormone ("LH") by the pituitary gland, decrease serum estrogens to castrated levels (Nicholson et al., Brit. J. Cancer 39, 268-273, 1979).

Several studies show that treatment of premenopausal breast cancer patients with LHRH agonists induces responses comparable to those achieved with other forms of castration (Klijn et al., J. Steroid Biochem. 20 1381, 1984; Manni et al., Endocr. Rev. 7: 89-94; 1986). Beneficial effects of treatment with LHRH agonists have also been observed in postmenopausal women (Nicholson et al., J. Ster. Biochem. 23, 843-848, 1985).

A.V. Schally et al., Cancer Treatment Reports, 68 (No. 1) 281-289 (1984), summarize the results of animal and clinical studies on growth inhibition of hormone-dependent mammary and prostate tumors by use of

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analogues of luteinizing hormone-releasing hormone, the so-called LHRH agonists and suggest that LHRH analogs and/or antagonists may have potential for treating breast cancer.

T.W. Redding and A.V. Schally, Proc. Natl Acad. Sci. USA, 80, 1459-1462 (1983) disclose reduction of estrogen-dependent mammary tumors in rats and mice by use of an LHRH agonist (D-Trp<sup>6</sup>]LHRH or of two specific antagonists.

In U.S. Pat. No. 4,071,622, it is disclosed that use of certain LHRH agonists causes regression of DMBA-induced mammary carcinoma in rats.

U.S. Pat. No. 4,775,660 relates to the treatment of female breast cancer by use of a combination therapy comprising administering an antiandrogen and an antiestrogen to a female after the hormone output of her ovaries has been blocked by chemical or surgical means.

U.S. Pat. No. 4,775,661 relates to the treatment of female breast cancer by use of a therapy comprising administering to a female after the hormone output of her ovaries has been blocked by chemical or surgical means an antiandrogen and optionally an inhibitor of sex steroid biosynthesis.

U.S. Pat. No. 4,760,053 describes a treatment of selected sex steroid dependent cancers which combines an LHRH agonist and/or an antiandrogen and/or an antiestrogen and/or at least one inhibitor of sex steroid biosynthesis.

In U.S. Pat. No. 4,472,382, it is disclosed that prostatic adenocarcinoma, benign prostatic hypertrophy and hormone-dependent mammary tumors may be treated with various LH-RH agonists and that prostate adenocarcinoma and benign hypertrophy may be treated by use of various LHRH agonists and an antiandrogen. However, there is no suggestion or disclosure of the present invention.

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Some clinical improvement in premenopausal women with breast cancer by use of the two LHRH agonists, Buserelin and Leuprolide, is also reported by H.A. Harvey et al. "LH-RH analogs in the treatment of human breast cancer", LHRH and its Analogs - A new Class of contraceptive and therapeutic Agents (B.H. Vickery and J.J. Nestor, Jr., and E.S.E. Hafez, eds) Lancaster, MTP Press, (1984), and by J.G.M. Klijn et al. "Treatment with luteinizing hormone-releasing hormone analogue (Buserelin) in premenopausal patients with metastatic breast cancer", Lancet 1, 1213-1216 (1982).

Androgen receptors have been demonstrated in human breast cancer samples (Engelsman et al., Brit. J. Cancer 30, 177, 1975; Lippman et al., Cancer 38, 868-874, 1976; Maass et al., J. Steroid Biochem. 6, 743-749, 1975) and in human breast cancer cell lines including MCF-7 cells (Lippman et al., Cancer Res. 36, 4610-4618, 1976). Recent reports have indicated that androgen receptors may add to the selective power of estrogen receptors (ER) or even supplant ER towards predicting response to endocrine therapy (Bryan et al., Cancer 54, 2436-2440, 1984; Teulings et al., Cancer Res. 40: 2557-2561, 1980).

The first androgen successfully used in the treatment of advanced breast cancer is testosterone propionate (Nathanson, Rec. Progr. Horm. Res. 1, 261-291, 1947). Many studies subsequently confirmed the beneficial effect of androgens on breast cancer (Adair, Surg. Gynecol. Obstet. 84, 719-722, 1947; Alan and Herrman, Ann. Surg. 123, 1023-1035, 1946; Adair et al., JAMA 140, 1193-2000, 1949). These initial results stimulated cooperative studies on the effect of testosterone propionate and DES which were both found to be effective in producing objective remissions. (Subcommittee on Steroids and Cancer of the Committee on Research of the

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Council on Pharmacy and Chemistry of the Am. Med. Association followed by the Cooperative Breast Cancer Group under the Cancer Chemotherapy National Service Center of the NCI who found that testosterone propionate improved remission rate and duration, quality of life and survival (Cooperative Breast Cancer Group, JAMA 188, 1069-1072, 1964).

A response rate of 48% (13 of 27 patients) was observed in postmenopausal women who received the long-acting androgen methenolone enanthate (Kennedy et al., Cancer 21, 197-201, 1967). The median duration of survival was four times longer in the responders as compared to the non-responder group (27 versus 7.5 months). A large number of studies have demonstrated that androgens induce remission in 20 to 40% of women with metastatic breast cancer (Kennedy, Hormone Therapy in Cancer. Geriatrics 25, 106-112, 1970; Goldenberg et al., JAMA 223, 1267-1268, 1973).

The combination Fluoxymesterone and Tamoxifen has been shown to be superior to Tamoxifen alone. In fact, complete responses (CR) were seen only in the combination arm while 32% showed partial response (PR) in the combination arm versus only 15% in the monotherapy arm. In addition, there were only 25% non-responders in the combination therapy arm versus 50% in the patients who received TAM alone (Tormey et al., Ann. Int. Med. 98, 139-144, 1983). Moreover, the median time from onset of therapy to treatment failure was longer with Fluoxymesterone + Tamoxifen (180 days) compared to the Tamoxifen arm alone (64 days). There was a tendency for improved survival in the combination therapy arm (380 versus 330 days).

The independent beneficial effect of an antiestrogen combined with an androgen is suggested by the report that patients who did not respond to Tamoxifen could respond to Fluoxymesterone and vice versa. Moreover, patients treated with Tamoxifen and crossing over to Fluoxymesterone

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survived longer than the reverse regimen (Tormey et al., Ann. Int. Med. 98, 139-144, 1983). Recent in vitro studies compose the relative anti-proliferative activities of an antiestrogen and an androgen on the growth of the estrogen-sensitive human mammary carcinoma cell line ZR-75-1 (Poulin et al. "Androgens inhibit basal and estrogen-induced cell proliferation in the ZR-75-1 human breast cancer cell line", Breast Cancer Res. Treatm. 12, 213-225, 1989a).

A response rate of 39% with an average duration of 11 months has recently been observed in a group of 33 postmenopausal women who previously failed or did not respond to Tamoxifen (Manni et al., Cancer 48: 2507-2509, 1981) upon treatment with fluoxymesterone (Halostatin) (10 mg, b.i.d.). Of these women, 17 had also undergone hypophysectomy. There was no difference in the response rate to Fluoxymesterone in patients who had previously responded to Tamoxifen and in those who had failed. Of the 17 patients who had failed to both Tamoxifen and hypophysectomy, 7 responded to Fluoxymesterone for an average duration of 10 months. Among these, two had not responded to either Tamoxifen and hypophysectomy.

Since testosterone propionate had beneficial effects in both pre- and postmenopausal women (Adair et al., J. Am. Med. Ass. 15: 1193-1200; 1949), it indicates that in addition to inhibiting gonadotropin secretion, the androgen exerts a direct inhibitory effect on cancer growth.

As mentioned above, Poulin et al. (Breast Cancer Res. Treatm. 12, 213-225, 1989a) have found that the growth of ZR-75-1 human breast carcinoma cells is inhibited by androgens, the inhibitory effect of androgens being additive to that of an antiestrogen. The inhibitory effect of androgens on the growth of human breast carcinoma cells ZR-75-1 has also been observed in vivo in nude mice.

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Many clinical trials have shown the benefits of medroxyprogesterone acetate ("MPA") in breast cancer therapy (Cavalli et al., J. Clin. Oncol. 2, 414, 1984; Van Veelen et al., Cancer 58, 713, 1986; Johnson et al., Brit. J. Cancer 50, 363, 1984; Rabustelli della Cuna, G. Comprehensive guide to the therapeutic use of medroxyprogesterone acetate in oncology, Farmitalia Carlo Erba, S.P.A., 1987).

Poulin et al. "Androgen and glucocorticoid receptor-mediated inhibition of cell proliferation by medroxyprogesterone acetate in ZR-75-1 human breast cancer cells", Breast Cancer Res. Treatm., 1989b, in press) have recently found that the inhibitory effect of medroxyprogesterone acetate (MPA) on the growth of the human ZR-75-1 breast cancer cells is mainly due to the androgenic properties of the compound. The androgenic properties of MPA have been clearly demonstrated in other systems (Labrie, C. et al., J. Steroid Biochem. 28: 379-384, 1987; Luthy et al., J. Steroid Biochem. 31: 845-852, 1988; Plante et al., J. Steroid Biochem., 31, 61-64, 1988). Other synthetic progestins have also been shown to possess, in addition to their progesterone-like activity, various degrees of androgenic activity (Labrie et al., Fertil. Steril. 31, 29-34, 1979; Poyet and Labrie, The Prostate 9, 237-246, 1986; Labrie, C. et al., J. Steroid Biochem. 28: 379-384, 1987; Luthy et al., J. Steroid Biochem. 31: 845-852, 1988; Plante et al., J. Steroid Biochem. 31, 61-64, 1988).

Poulin et al. "Inhibition of estrogen-dependent cell proliferation by the synthetic progestin R5020 and antagonism of progestin action by insulin in ZR-75-1 human breast cancer cells", Breast Cancer Res. Treatm., 1989c, in press) have observed that 17,21-dimethyl-19-nor-4,9-pregnadiene-3,20-dione ("R5020, promegestone") and progesterone itself can inhibit the growth of the human breast cancer cell line

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ZR-75-1 by an action mediated by the progesterone receptor. R5020 has been found to inhibit the growth of normal human breast cancer cells in culture in the presence as well as in the absence of  $E_2$  (Gompel et al., J. Clin. Endocrinol. Metab. 63, 1174-1180, 1986).

H. Mouridsen et al., Cancer Treatm. Rev. 5, 131-141, (1978), disclose that Tamoxifen, an antiestrogen, is effective in remission of advanced breast cancer in about 30% of the women patients treated.

J.G.M. Klijn et al., (J. Steroid Biochem., 20 (No. 6B), 1381 (1984), disclosed the combined use of the antiestrogen, Tamoxifen, and the LHRH agonist, Buserelin, for treatment of breast cancer is known but objective remission of such cancers remains low (35%).

Various steroids have been described as irreversible aromatase inhibitors, including 4-hydroxy-4-androstene-3,17-dione (Brodie et al., Steroids 38: 693-702, 1981; Covey and Hood, Cancer Res. 42; Suppl. 3327s-3333s, 1982), androsta-4,6-triene-3,17-dione (Covey and Hood, Endocrinology 108, 1597-1599, 1981), MDL 18962 (Johnston et al., Endocrinology 115, 776-785, 1984), SH 489 (Henderson et al., J. Steroid Biochem. 24, 303-306, 1986) and 6-methylenandrosta-1,4-diene-3,17-dione ("FCE 24304") (Giudici et al., J. Steroid Biochem. 30: 391-394, 1988).

Huggins and Bergenstal (Cancer Res. 12, 134-141, 1952) have observed that adrenalectomy could induce remission in breast cancer patients who had failed after castration. Treatment of advanced breast cancer with aminoglutethimide after therapy with the antiestrogen Tamoxifen is disclosed by A.V. Buzdar et al. Cancer 50, 1708-1712 (1982).

High doses of ketoconazole can inhibit  $17\alpha$ -hydroxylase and C17-20-lyase (Santen et al., J. Clin. Endocrinol. Metab. 57, 732-736, 1983) while 16-methylene estrone can inhibit the  $17\beta$ -HSD step (Thomas et al., J. Biol. Chem. 258, 11500-11503, 1983).

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Trilostane and epostane have been described as inhibitors of  $3\beta$ -hydroxy-steroid dehydrogenase activity (Ernshaw et al., Clin. Endocrinol. 21, 13-21, 1984; Robinson et al., J. Steroid Biochem. 21, 601-605, 1984; Lambert et al., Ann. Clin. Biochem. 23, 225-229, 1986; Potts et al., Steroids 32, 257-267, 1978) and have been successfully used for the treatment of breast cancer in combination with corticosteroids (Beardwell et al., Cancer Chemother. Pharmacol. 10: 158-160, 1983; Williams et al., Cancer Treat. Rep. 71, 1197-1201, 1987).

4-MA, (17 $\beta$ -N,N-diethylcarbamoyl-4-methyl-4-aza-5 $\alpha$ -androstan-3-one) has been found to inhibit  $3\beta$ -hydroxysteroid dehydrogenase activity in granulosa cells (Chan et al., Biochem. Biophys. Res. Commun. 144, 166-171, 1987). Epostane has been shown to inhibit  $3\beta$ -hydroxysteroid dehydrogenase activity in pregnant goats (Taylor, J. Endocrinol. 113, 489-493, 1987).

A synthetic androgen, methyltrienolone has been reported to inhibit the growth of endometrial carcinoma cells in culture (Centola, Cancer Res. 45: 6264-6267, 1985). Medroxyprogesterone acetate is successfully used for the treatment of endometrial cancer (Ayoub et al., Gynecol. Oncol. 31(2): 327-337, 1988).

Prolactin and growth hormone have been shown to stimulate colony formation of the NMU rat mammary tumor cultured in vitro in the soft agar clonogenic assay (Manni and Wright, J. Natl Cancer Inst. 74, 941-944, 1985).

Prolactin is known to play a role in stimulating carcinoma in experimental animals, especially mammary carcinoma induced in the rat by dimethylbenz(a)anthracene (DMBA) (Welch et al., Cancer Res. 30, 1024-1029 1970). A study of 30 women suffering from breast cancer showed

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that 10 became pain-free upon treatment with L-Dopa, an inhibitor of prolactin secretion (Minton, Cancer 33, 358-363, 1974). In these 10 women, there were objective and subjective signs of tumor control.

A problem with prior art treatments is a lack of effective simultaneous control of both beneficial and detrimental hormones. Moreover, effective control of detrimental hormones (i.e. those hormones which may stimulate tumor growth) often requires closing down a plurality of pathways. Prior art treatments have tended to foreclose only particular synthetic pathways, leaving other pathways available for formation of the undesired hormone. Other treatments have attempted to block the activity of detrimental hormones such as estrogens. However, because such blocking is difficult to completely achieve, the formation of the estrogens, together with incomplete blocking, enables some estrogens to bind and undesirably activate receptors. This necessarily diminishes the effectiveness of treatment.

#### SUMMARY OF THE INVENTION

It is an object of the present invention to provide combination therapy for the treatment of breast cancer and endometrial cancer wherein the treatment selectively inhibits the formation and/or action of hormones which would otherwise contribute to tumor growth, while maintaining those which do not increase growth and are otherwise beneficial to general health.

It is another object of the invention to provide combination therapy having increased effectiveness in slowing or reversing tumor growth.

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It is another object of the invention to provide therapy for treating breast or endometrial cancer having significantly reduced frequency of unwanted side effects.

It is a further object of the invention to provide kits having a combination of pharmaceutical compositions which may be effectively utilized together for carrying out the novel combination therapies of the invention.

It is another object of the invention to provide a novel pharmaceutical composition which is effective, in and of itself, for utilization in a beneficial combination therapy because it includes a plurality of active ingredients which may be utilized in accordance with the invention.

These and other objects are achieved by providing a method of treating breast or endometrial cancer in a warm-blooded animal wherein said method comprises inhibiting the ovarian hormonal secretions of said animal and administering to said animal therapeutically effective amounts of an antiestrogen and at least one compound selected from the group consisting of an androgen, a progestin, an inhibitor of sex steroid formation, an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.

The invention further provides a method for treating breast or endometrial cancer in a warm-blooded animal in need of such treatment which comprises administering to such animals a therapeutically effective amount of an antiestrogen and at least one compound selected from the group consisting of an inhibitor of sex steroid formation, an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion, an inhibitor of adrenal corticotrophin hormone secretion and a progestin.

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The invention further provides a kit for treatment of breast or endometrial cancer, said kit including a pharmaceutical composition comprising an antiestrogen and at least one pharmaceutical composition selected from the group consisting of a pharmaceutical composition comprising a progestin, a pharmaceutical composition comprising an inhibitor of sex steroid formation, a pharmaceutical composition comprising an inhibitor of prolactin secretion, a pharmaceutical composition comprising an inhibitor of ACTH secretion and a pharmaceutical composition comprising an inhibitor of growth hormone secretion.

The invention further provides a therapeutic composition for treating breast or endometrial cancer in a warm-blooded animal which comprises an ovarian secretion inhibitor, an antiestrogen, and at least one compound selected from the group consisting of an androgen, a progestin, an inhibitor of sex steroid formation, an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.

The invention contemplates that any of the active ingredients discussed herein may be utilized in combination with diluents and other carriers, for oral or parenteral administration, or may be delivered by any conventional delivery system. In certain preferred embodiments, active ingredients necessary to the combination therapy described above may be combined in a single pharmaceutical composition for simultaneous administration.

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## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Figure 1 is a schematic representation of the sites of action of drugs active in the treatment of breast cancer. The following abbreviations are used: ER: estrogen receptor; AR: androgen receptor; PR: progesterone receptor; GR: glucocorticoid receptor; DHEAS: dehydroepiandrosterone sulfate; DHEA: dehydroepiandrosterone;  $\Delta^5$ -diol androst-5-ene-3 $\beta$ ,17 $\beta$ -diol;  $\Delta^4$ -dione, androstenedione;  $E_1$ : estrone;  $E_2$ : 17 $\beta$ -estradiol; T: testosterone; DHT: dihydrotestosterone;  $E_2$ S:  $E_2$ -sulfate;  $E_1$ -S:  $E_1$  sulfate; (1) LHRH-A: luteinizing hormone-releasing hormone agonist or antagonist; (2) ANTI-E: antiestrogen; (3) AND: androgen; (4) PROG: progestin; (5) 17 $\beta$ -HSD: inhibitor of 17 $\beta$ -estradiol steroid dehydrogenase or 17 $\beta$ -hydroxysteroid dehydrogenase; (6) ARO: inhibitor of aromatase activity; (7) 3 $\beta$ -HSD: inhibitor of 3 $\beta$ -hydroxysteroid,  $\Delta^5$ - $\Delta^4$  isomerase; (8) INH: inhibitor of adrenal steroidogenesis; (9) PRL: inhibitor of prolactin secretion; (10) GH: inhibitor of growth hormone secretion; (11) ACTH: inhibitor of ACTH secretion.

Referring to Figure 1, the "+"s and "-"s next to each indicated receptor designate whether activation of that receptor aids or hinders tumor growth. As may be seen from Figure 1, activation of the estrogen receptor will stimulate tumor growth, and is therefore to be prevented. However, it is important to continue to activate the androgen receptor, whose activation may inhibit tumor growth. Likewise, it is desirable to continue to activate the progesterone and glucocorticoid receptors.

One method of inhibiting activation of the estrogen receptor is treatment with an effective antiestrogen compound having an affinity for the receptor site such that it binds the receptor site and

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blocks estrogen from binding and activating the site. It is important to select antiestrogens which tend to be pure antagonists, and which have no agonistic activity. Otherwise, the antiestrogen which blocks the receptor site from estrogen, may itself activate the site. Preferred antiestrogens are discussed in detail below. Because it is extremely difficult to block all receptor sites, it is desirable to simultaneously decrease the concentration of estrogen available to activate estrogen receptors. Hence, it is desirable to inhibit production of estrogen by the ovaries. This may be accomplished in a variety of ways including surgical removal of the ovaries, irradiation of the ovaries, or by chemical means. Chemical means include but are not limited to the use of agonists or antagonists of luteinizing hormone releasing hormone. These compounds act on the pituitary in a manner effective to stop its production of bioactive luteinizing hormone, a hormone necessary to cause the ovaries to produce and secrete estrogen and/or other hormones which may be converted to estrogen.

As may be seen from the scheme of Figure 1, a number of hormones released by the adrenals may be converted by a variety of biological pathways into estrogen. Among the estrogens thus produced are  $17\beta$ -estradiol and androst-5-ene- $3\beta$ , $17\beta$ -diol. It is therefore highly desirable to include an inhibitor of  $17\beta$ -estradiol dehydrogenase or  $17\beta$ -hydroxy steroid dehydrogenase. Such inhibitors close down the synthetic pathways crossed by vertical line 5 denoted " $17\beta$ -HSD" on Figure 1. Hence synthesis of both major forms of estrogen shown on Figure 1 is substantially prevented. Other sex steroid formation inhibitors such as inhibitors of  $3\beta$ -hydroxy steroid or of aromatase activity are also preferably

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included in treatment in order to close down the synthetic pathways crossed by the two horizontal lines 6 and 7 denoted "ARO" and " $3\beta$ -HSD", respectively.

It will be noted that the foregoing methods of inhibiting estrogen synthesis also have the undesirable effect of inhibiting androgen synthesis. Because androgens are beneficial to retarding tumor growth, it is desirable to administer ("add block") androgens in connection with any of the foregoing treatments which inhibit sex steroid synthesis. Other preferred additions to treatment include progestins, inhibitors of growth hormone secretion, inhibitors of prolactin secretion and inhibitors of adrenal corticotrophin hormone secretion. The latter has the effect of preventing ACTH from reaching the adrenals and thus of preventing the adrenals from synthesizing and secreting compounds such as dehydroepiandrosterone sulfate, a precursor of the synthesis of estrogen. Alternatively, inhibitors which close down synthetic pathways in the adrenals will achieve the same result. When adrenal secretions are inhibited or stopped, essential glucocorticoids should be added back as part of the therapy.

In one embodiment, the invention provides a method of treating breast and endometrial cancer in a warm-blooded animal in need of such treatment which may comprise inhibiting the ovarian hormonal secretions of said animal by surgical, radiotherapeutical or chemical means and administering to said animal therapeutically effective amounts of an antiestrogen and at least one compound selected from the group consisting of an androgen, a progestin, at least one inhibitor of sex steroid formation, one inhibitor of prolactin secretion, one inhibitor of growth hormone and one inhibitor of ACTH secretion or mixtures thereof.

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In certain embodiments, the invention provides a method of treating breast cancer which comprises administering a therapeutically effective amount (1) of an antiestrogen and a progestin, (2) of an antiestrogen and at least one inhibitor of sex steroid biosynthesis, (3) of an antiestrogen, an androgen and a progestin, (4) of an antiestrogen, an androgen and at least one inhibitor of sex steroid biosynthesis, (5) of an antiestrogen, a progestin and at least one inhibitor of sex steroid biosynthesis, (6) of an antiestrogen, an androgen, a progestin and at least one inhibitor of sex steroid biosynthesis, (7) of an antiestrogen, an androgen, and at least one inhibitor of prolactin secretion and/or growth hormone secretion and/or ACTH secretion, (8) an antiestrogen, a progestin and at least one inhibitor of prolactin secretion and/or growth hormone secretion and/or ACTH secretion, (9) an antiestrogen, at least one inhibitor of sex steroid formation and at least one inhibitor of prolactin secretion and/or growth hormone secretion and/or ACTH secretion, (10) an antiestrogen, an androgen, a progestin and at least one inhibitor of prolactin secretion and/or growth hormone secretion and/or ACTH secretion, (11) an antiestrogen, an androgen, at least one inhibitor of sex steroid formation and at least one inhibitor of prolactin secretion and/or growth hormone and/or ACTH secretion, (12) an antiestrogen, a progestin, at least one inhibitor of sex steroid formation and at least one inhibitor of prolactin secretion and/or growth hormone secretion and/or ACTH secretion, (13) an antiestrogen, an androgen, a progestin, at least one inhibitor of sex steroid formation and at least one inhibitor of prolactin secretion and/or growth hormone secretion and/or ACTH secretion.

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In one aspect, the invention provides a method of treating breast or endometrial cancer in a warm-blooded female animal in need of such treatment which comprises administering to said animal whose hormone output of the ovaries is blocked, a therapeutically effective amount of an antiestrogen, an androgen and a blocker of steroid biosynthesis or a pharmaceutical composition thereof. The ovarian hormonal secretions of said animal can be blocked by surgical or chemical means. In one aspect, the invention provides a method of treating cancer in a castrated warm-blooded female animal (i.e., one whose ovaries are blocked by surgical or chemical means from secreting estrogen) which comprises administering an antiestrogen and an androgen or pharmaceutical compositions thereof, in amounts sufficient to treat such cancers.

In certain embodiments, the ovaries may be surgically removed (oophorectomy) but preferably the secretion of hormones from the ovaries is blocked chemically by administering an effective amount of an LHRH agonist or antagonist. In one preferred aspect, the present invention provides a method of treating breast and endometrial cancer in a warm-blooded animal, which comprises administering to an animal in need of such treatment an LHRH agonist or antagonist, an antiestrogen, an androgen, and at least one inhibitor of sex steroid formation, or pharmaceutical compositions thereof, in amounts sufficient to treat breast and endometrial cancer.

In its preferred aspect, the LHRH agonist is administered parenterally (subcutaneously or intramuscularly) and the androgen, antiestrogen, and at least one inhibitor of sex steroid formation are each administered orally. The invention also provides kits or single packages combining the preferred pharmaceutical compositions of the invention. For example, a

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three-component kit provides an LHRH agonist parenteral pharmaceutical composition, an androgen oral pharmaceutical composition and an antiestrogen oral composition. A four-component kit may provide, for example, an LHRH agonist parenteral pharmaceutical composition, an antiestrogen oral pharmaceutical composition, an androgen oral composition and a steroid biosynthesis inhibitor oral composition. In certain preferred embodiments, the antiestrogen itself also acts as a sex steroid inhibitor, and the kit need only contain one pharmaceutical composition for achieving both functions.

Thus, this invention provides a novel method for effective treatment of breast and endometrial cancer. In addition, the amounts of antiestrogen administered in this combined therapy are lower than normally used in the prior art, e.g., J.G.M. Klijn et al., J. Steroid Biochem. 20 (no. 6B) 1381 (1984), to treat breast cancer, and thus, the harmful effects of relatively large doses of antiestrogen are minimized.

By combining an optimal blockade of estrogen formation and/or action and the inhibitory effect of androgens on breast and endometrial cancer cell growth, the present invention provides a method of maximally inhibiting the growth of breast and endometrial cancer.

In female mammals, the ovaries may be surgically removed (oophorectomy) or irradiated. However, it is preferred that secretion of estrogens from the ovaries be blocked by chemical castration, for example, by administering an effective amount of an LHRH agonist or antagonist.

In its preferred aspect, the LHRH agonist is administered parenterally (subcutaneously or intramuscularly or intranasally) and, in association therewith, the antiestrogen, the androgen and the inhibitor of sex

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steroid biosynthesis are each administered orally. Thus, this invention provides a novel method for effective treatment of breast and endometrial cancer. In another preferred aspect, the antiestrogen, androgen and/or inhibitor of sex steroid biosynthesis are administered in a controlled release formulation.

In one preferred aspect, the present invention provides an effective method of treating breast and endometrial cancer in warm-blooded female animals in need of such treatment by administering an LHRH agonist or antagonist, in association with an antiestrogen, a progestin, an androgen and an inhibitor of sex steroid biosynthesis or pharmaceutical compositions thereof in amounts sufficient to inhibit tumor growth. These active compounds can be administered together or in any order as discussed hereinafter.

To assist in determining the effect of the treatment, blood plasma concentrations of the sex steroids of adrenal and ovarian origin, i.e., precursor steroids, androgens and estrogens, and tumor size are measured. Lowered concentrations of sex steroids and reduction in tumor size are indicative of successful treatment, e.g. inhibition of tumor growth using active compounds described herein in accordance with the present invention. The concentrations of adrenal androgens and estrogens such as dehydroepiandrosterone (DHEA), DHEA-S sulfate (DHEAS), androst-5-ene-3 $\beta$ ,17 $\beta$ -diol ( $\Delta^5$ -diol) and, the ovarian estrogen, 17 $\beta$ -estradiol ( $E_2$ ) are measured by standard methods well known to those skilled in the art, see for example, F. Labrie et al., The Prostate 4, 579-584, 1983; Luthy et al., J. Gynecol. Endocrinol., 1, 151-158, 1987).

The change in tumor size is measured by standard physical methods well known to those skilled in the art, e.g., bone scan, chest X-ray, skeletal survey, ultrasonography of the liver and liver scan (if needed), CAT-scan and physical examination.

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While a LHRH agonist or a LHRH antagonist may be used in one preferred aspect of the present invention, the use of a LHRH agonist is more preferred.

By the term "LHRH agonist" is meant synthetic analogues of the natural luteinizing hormone-releasing hormone (LHRH), for example, a decapeptide of the structure: L-pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-glycyl-L-leucyl-L-arginyl-L-propylglycyl-NH<sub>2</sub>. Suitable LHRH agonists include nonapeptides and decapeptides represented by the formula: L-pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-X-Y-arginyl-L-prolyl-Z

wherein X is D-tryptophyl, D-leucyl, D-alanyl, iminobenzyl-D-histidyl, 3-(2-naphthyl)-D-alanyl, O-tert-butyl-D-seryl, D-tyrosyl, D-lysyl, D-phenylalanyl or N-methyl-D-alanyl and Y is L-leucyl, D-leucyl, N<sup>α</sup>-methyl-D-leucyl, N<sup>α</sup>-methyl-L-leucyl or D-alanyl and

wherein Z is glycyl-NHR<sub>1</sub> or NHR<sub>1</sub> wherein R<sub>1</sub> is H, lower alkyl or lower haloalkyl. Lower alkyl includes straight- or branched-chain alkyls having 1 to 6 carbon atoms, e.g., methyl, ethyl, propyl, pentyl or hexyl, isobutyl, neopentyl and the like. Lower haloalkyl includes straight- and branched-chain alkyls of 1 to 6 carbon atoms having a halogen substituent, e.g., -CF<sub>3</sub>, -CH<sub>2</sub>CF<sub>3</sub>, -CF<sub>2</sub>CH<sub>3</sub>. Halogen means F, Cl, Br, I with Cl being preferred.

In preferred nonapeptides, Y is L-leucyl, X is an optically active D-form of tryptophan, serine (t-BuO), leucine, histidine (iminobenzyl), and alanine.

Preferred decapeptides include [D-Trp<sup>6</sup>]-LHRH wherein X=D-Trp, Y=L-leucyl, Z=glycyl-NH<sub>2</sub>, [D-Phe<sup>6</sup>]-LHRH wherein X=D-phenylalanyl, Y=L-leucyl and Z=glycyl-NH<sub>2</sub> or [D-Nal(2)<sup>6</sup>]-LHRH which is [(3-(2-naphthyl)-D-Ala<sup>6</sup>)-LHRH wherein X=3-(2-naphthyl)-D-alanyl, Y=L-leucyl and Z=glycyl-NH<sub>2</sub>).

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Other LHRH agonists useful within the scope of this invention are the  $\alpha$ -aza analogues of the natural LH-RH, especially, [D-Phe<sup>6</sup>, Azgly<sup>10</sup>]-LHRH, [D-Tyr(Me)<sup>6</sup>, Azgly<sup>10</sup>]-LHRH, and [D-Ser-(t-BuO)<sup>6</sup>, Azgly<sup>10</sup>]-LHRH disclosed by A.S. Dutta et al. in J. Med. Chem., 21, 1018 (1978) and U.S. Pat. No. 4, 100,274 as well as those disclosed in U.S. Pat. Nos. 4,024,248 and 4,118,483.

Typical suitable LHRH antagonists include [N-Ac-D-p-Cl-Phe<sup>1,2</sup>, D-Phe<sup>3</sup>, D-Arg<sup>6</sup>, D-Ala<sup>10</sup>]-LHRH disclosed by J. Ercheggi et al., Biochem. Biophys. Res. Commun. 100, 915-920, (1981); [N-Ac-D-p-Cl-Phe<sup>1,2</sup>, D-Trp<sup>3</sup>, D-Arg<sup>6</sup>, D-Ala<sup>10</sup>]-LHRH disclosed by D.H. Coy et al., Endocrinology, 110: 1445-1447, (1982); [N-Ac-D-(3-(2-naphthyl)-Ala)<sup>1</sup>, D-p-Cl-Phe<sup>2</sup>, D-Trp<sup>3</sup>, D-hArg(Et)<sup>6</sup>, D-Ala<sup>10</sup>]-LHRH and [N-Ac-Pro<sup>1</sup>, D-p-F-Phe<sup>2</sup>, (D-(3-(2-naphthyl)Ala)<sup>3,6</sup>]-LHRH disclosed by J.J. Nestor et al. J. Steroid Biochem., 20 (No. 6B), 1366 (1984); the nona- and decapeptides analogs of LHRH useful as LHRH antagonists disclosed in U.S. Pat. No. 4,481,190 (J.J. Nestor et al.); analogs of the highly constrained cyclic antagonist, cycle [ $\Delta^3$ Pro<sup>1</sup>, D-p-Cl-Phe<sup>2</sup>, D-Trp<sup>3,6</sup>, N-Me-Leu<sup>7</sup>,  $\beta$ -Ala<sup>10</sup>]-LHRH disclosed by J. Rivier, J. Steroid Biochem., 20, (No. 6B), 1365 (1984), and [N-Ac-D-(3-(2-naphthyl)-Ala<sup>1</sup>, D-p-F-Phe<sup>2</sup>, D-Trp<sup>3</sup>, D-Arg<sup>6</sup>]-LHRH disclosed by A. Corbin et al., J. Steroid Biochem. 20 (No. 6B) 1369 (1984).

Other LHRH agonist and antagonist analogs are disclosed in LHRH and its Analogues (B.H. Vickery et al. editors at page 3-10 (J.J. Nestor), 11-22 (J. Rivier et al.) and 23-33 (J.J. Nestor et al.)).

The LHRH agonists and antagonists useful in this invention may conveniently be prepared by the method described by Stewart et al. in "Solid Phase Peptide Synthesis" (published in 1969 by Freeman & Co., San Francisco, page 1) but solution synthesis may also be used.

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The nona- and decapeptides used in this invention are conveniently assembled on a solid resin support, such as 1% cross-linked Pro-Merri-field resin by use of an automatic peptide synthesizer. Typically, side-chain protecting groups, well known to those in the peptide arts, are used during the dicyclohexylcarbodiimide-catalyzed coupling of a tert-butyloxycarbonylamino acid to the growing peptide attached to a benzhydrylamine resin. The tert-butyloxycarbonyl protecting groups are removed at each stage with trifluoroacetic acid. The nona- or decapeptide is cleaved from the resin and deprotected by use of HF. The crude peptide is purified by the usual techniques, e.g., gel filtration, HPLC and partition chromatography and optionally lyophilization. See also D.H. Coy et al., J. Med. Chem. 19, pages 423-452, (1976).

Typically suitable androgens include 6- $\alpha$ -methyl,17- $\alpha$ -acetoxy progesterone or medroxyprogesterone acetate available, among others, from Upjohn and Farmitalia Carlo Erba, S.p.A. under the trade names, among others, of Provera and Farlutal, and the acronym MPA.

Other suitable androgens include other synthetic progestins as described in Labrie et al. (Fertil. Steril. 31: 29-34, 1979) as well as anabolic steroids or "progestins" (Raynaud and Ojasoo, in: Innovative Approaches in Drug Research. Elsevier Sc. Publishers, Amsterdam, pp. 47-72, 1986; Sandberg and Kirdoni, Pharmac. Ther. 36: 263-307, 1988; and Vincens, Simard and De Lignières, Les Androgènes. In: Pharmacologie Clinique, Base de Thérapeutique, 2ième édition, Expansion Scientifique (Paris), pp. 2139-2158, 1988), as well as Calusterone (7 $\beta$ ,17 $\alpha$ -dimethyl-testosterone), anabolic steroids (Lamb, Am. J. Sports Medicine 12, 31-38, 1984; Hilf, R. Anabolic-androgenic steroids and experimental tumors. In: (Kochachian, C.D., ed.), Handbook of Experimental Pharmacology, vol. 43,

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Anabolic-Androgenic Steroids, Springer-Verlag, Berlin, 725 pp., 1976), fluoxymesterone (9 $\alpha$ -fluoro-11 $\beta$ -hydroxy-17 $\alpha$ -methyl testosterone), testosterone 17 $\beta$ -cypionate, 17 $\alpha$ -methyltestosterone, Pantestone (testosterone undecanoate),  $\Delta^1$ -testololactone and Andractim.

Typically suitable progestins include 17,21-dimethyl-19-nor-4,9-pregnadiene-3,20-dione ("R5020, promegestone") available from Roussel-UCLAF as well as cyproterone acetate (Androcur) available from Schering AG, 6-alpha-methyl, 17-alpha-acetoxy progesterone or medroxyprogesterone acetate (MPA) available from, among others, Upjohn and Farmitalia, Calbo Erba, Gestoden available from Shering, megestrol acetate (17 $\alpha$ -acetoxy-6-methyl-pregna-4,6-diene-3,20-dione) available from Mead Johnson & Co., Evansville, Ind., under the trade name of Megace. Other progestins include Levonorgestrel, Gestodene, desogestrel, 3-keto-desogestrel, norethindrone, norethisterone, 13 $\alpha$ -ethyl-17-hydroxy-18,19-dinor-17 $\beta$ -pregna-4,9,11-triene-20-yn-3-one (R2323), demegestone, norgestrienone, gastrinone, progesterone itself and others described in Raynaud and Ojasoo, J. Steroid Biochem. 25: 811-833, 1986; Raynaud et al., J. Steroid Biochem. 12: 143-157, 1980; Raynaud, Ojasoo and Labrie, Steroid Hormones, Agonists and Antagonists, In: Mechanisms of Steroid Action (G.P. Lewis and M. Ginsburg, eds), McMillan Press, London, pp. 145-158 (1981).

Typical suitable antiestrogens include those steroidal and non-steroidal antiestrogens such as (1RS,2RS)-4,4'-diacetoxy-5,5'-difluoro-(1-ethyl-2-methylene)di-m-phenylenediacetate, which is available from Biorex under the trade name of Acefluranol, 6 $\alpha$ -chloro-16 $\alpha$ -methyl-pregna-4-ene-3,20-dione which is available from Eli Lilly & Co., Indianapolis, Ind. under the trade name of Clometheron, 6-chloro-17-hydroxypregna-1,4,6-triene-3,20-dione which is available as the acetate salt from Syntex

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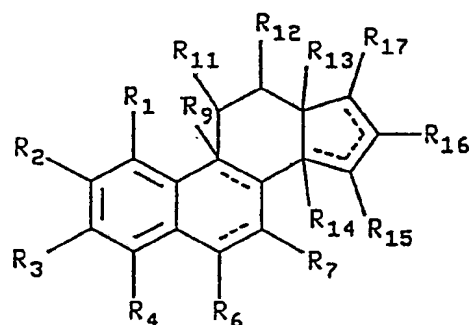
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Labs, Palo Alto, Cal. as Delmadione Acetate, 17-hydroxy-6-methyl-19-norpregna-4,6- diene-3,20-dione which is available from Theramex under the name of Lutenyl, 1-[2-[4-[1-(4-methoxyphenyl)-2-nitro-2-phenylethenyl]phenoxy]ethyl]-pyrrolidine which is available as the citrate salt from Parke-Davis Div. of Warner-Lambert Co., Morris Plains, N.J. under the name of Nitromifene Citrate, substituted aminoalkoxyphenylalkenes such as (Z)-2-[4-(1,2-diphenyl-1-butenyl)-phenoxy]-N,N-dimethylethanamine which is available as the citrate salt from Stuart Pharmaceuticals, Wilmington, Del. as Tamoxifen Citrate (see also Belgian patent No. 637,389, Mar. 1964), 3,4-dihydro-2-(p-methoxyphenyl)-1-naphthyl p-[2-(1-pyrrolidinyl)ethoxy]phenyl ketone which is available as the methane sulfonate salt from Eli Lilly & Co. under the tradename of Trioxifene Mesylate, 1-[4'-(2-phenyl)-b1-(3'-hydroxyphenyl)-2-phenyl-but-1-ene which is available from Klinge Pharma, [6-hydroxy-2-(p-hydroxyphenyl)-benzo(b)thien-3-yl]-[2-(1-pyrrolidinyl)-ethoxy phenyl]ketone which is available from Eli Lilly & Co. (LY 117018), [6-hydroxy-2-(4-hydroxyphenyl)benzo(b)thien-3-yl]-[4-(2-(1-piperidinyl)ethoxy)phenyl]methanone, which is available from Eli Lilly & Co. as the hydrogen chloride salt (LY156758) and meso-3,4-bis(3'-hydroxyphenyl) hexane as well as the dimethyl, dipropyl and 3'-acetoxy phenyl analogues which are described in U.S. Pat. No. 4,094,994 and a series of 1-phenyl-alkane and -alkenes, e.g. (E)-3-cyclopentyl-1-(4-hydroxyphenyl)-1-phenyl-1-butene and 2-cyclopentyl-1-[4-hydroxy- or methoxyphenyl]-3-phenyl-2-propen-1-ol and FC-1157 which is available as the citrate salt from Farnos Group, Ltd., Turku, Finland (see also Eur. Pat. Appln. EP. No 78,158). It is preferred to use an antiestrogen which shows minimal partial estrogen agonism.

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FC-1157, LY-117018, LY 156758 and Tamoxifen are at the preferred anti-estrogens of the class of those possessing some agonistic activity.

Suitable antiestrogens which also include 7 $\alpha$ -substituents of estradiol (European Pat. No. 0138504) and non-steroidal compounds bearing a similar aliphatic side-chain (U.S. Pat. 4732912) are represented by the general formula I:



wherein the dotted lines represent optional double bonds;

wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub> are independently selected from the group consisting of hydrogen, hydroxyl, alkylsulfonyl(lower)alkoxy, arylsulfonyl(lower)alkoxy, halogen, lower alkyl, lower alkoxy, lower alkylsilyl, amino and nitro;

wherein R<sub>7</sub> is selected from the group consisting of hydrogen, hydroxyl, halogen, lower alkyl, methoxy, ethoxy, propoxy, hydroxyethoxy, lower alkoxy, acetoxy, propionyloxy, butyryloxy, oenanthoyloxy, cypionoyloxy,

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trans-4-n-butyl-cyclohexanecarbonoyloxy,  $(C_2-C_{20})$ alkanoyloxy, lower alkoxy carbonyloxy, carboxy,  $(C_3-C_{20})$ alkenoyloxy,  $(C_3-C_{20})$ alkynoyloxy or  $(C_7-C_{10})$ aroyloxy; wherein  $R_6$  is selected from the group consisting of hydrogen, halogen, lower alkyl, amino and nitrile;

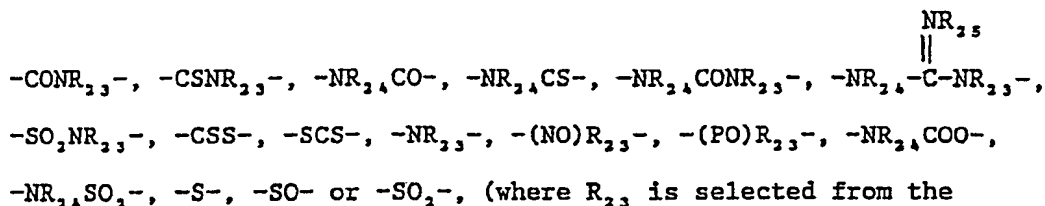
wherein  $R_7$  is in  $\alpha$  position and is hydrogen, hydroxyl, halogen, lower alkyl, lower alkoxy, lower alkylsilyl, amino, nitrile, nitro, nitroso, alkylsulfonyl, arylsulfonyl, lower alkylamino, di(lower)alkylamino, or is represented by the formulae  $AXR_{2,1}$  and  $A^1-[Y-A^{1,1}]_u-X-R_{2,1}$  wherein:

A is straight- or branched-chain  $(C_1-C_{30})$ alkylene,  $(C_2-C_{30})$ alkenylene,  $(C_2-C_{30})$ alkynylene or fluoro-substituted analogs of the foregoing; u is an integer from 0 to 5; wherein  $A^1$  and  $A^{1,1}$  may be the same or different and are selected from the group consisting of a bond, straight- or branched-chain alkylene, straight- or branched-chain alkynylene, straight- or branched-chain alkenylene, and fluoro-substituted analogs of the foregoing, wherein  $A^1$  and  $A^{1,1}$  together have a total of from 3 to 30 carbon atoms, and Y is selected from the group consisting of -O-, -S-, -Se-, -SO-, -SO<sub>2</sub>-, -CO-, -NR<sub>2,1</sub>-, -SiR<sub>2,1</sub>R<sub>2,1</sub>-, -CR<sub>2,1</sub>OR<sub>2,1</sub>-, -NR<sub>2,1</sub>CO-, -NR<sub>2,1</sub>CS-, -CONR<sub>2,1</sub>-, -CSNR<sub>2,1</sub>-, -COO-, -COS-, -SCO-, -CSS-, -SCS-, -OCO- and phenylene ( $R_{2,1}$  being hydrogen or lower alkyl);  $R_{2,1}$  is selected from the group consisting of hydrogen, straight- or branched-chain lower alkyl, lower alkenyl or lower alkynyl,  $(C_3-C_7)$ cycloalkyl, halogeno(lower)alkyl, carboxy(lower)alkyl, (lower)alkoxycarbonyl(lower)alkyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{11})$ arylalkyl, di(lower)alkylamino(lower)alkyl and fluoro-

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substituted analogs of the foregoing, and wherein X is



group consisting of hydrogen, lower alkyl, and a species which, together with  $\text{R}_{2,1}$ , forms a saturated or unsaturated heterocyclic ring having at least one nitrogen atom and, optionally, a second heteroatom selected from the group consisting of oxygen, sulfur, silicon, selenium, nitrogen and fluoro-substituted analogs of the foregoing, and where  $\text{R}_{2,4}$  is hydrogen or lower alkyl) wherein

$\text{R}_{2,5}$  is hydrogen, nitrile or nitro) ( $\text{XR}_{2,1}$  may form a tetrazole ring); wherein  $\text{R}_{1,1}$  is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl,  $(\text{C}_6-\text{C}_{10})$ aryl, alkylsulfonyl, arylsulfonyl, a substituted 5- to 7-member heterocyclic ring having at least one heteroatom (selected from oxygen, sulfur, silicon, selenium, nitrogen),  $-(\text{CH}_2)_s\text{W}$  (wherein W is nitrile, hydroxyl, azido, nitroso, nitro, thionitrile, halogen, alkylsulfonyl or arylsulfonyl, and s is an integer from 1 to 6),  $\text{OR}_{2,6}$  (wherein  $\text{R}_{2,6}$  is hydrogen, lower alkyl or  $(\text{C}_6-\text{C}_{10})$ aryl),  $\text{DR}_{2,7}$  (wherein D is  $-\text{Se}-$ ,  $-\text{NR}_{2,8}$ ,  $-\text{S}-$  or  $-\text{O}-$ , and  $\text{R}_{2,7}$  is hydrogen, lower alkyl),  $=\text{O}$ ,  $=\text{S}$ ,  $=\text{Se}$ ,  $=\text{NR}_{2,9}$  (wherein  $\text{R}_{2,9}$  is hydrogen or lower alkyl);

wherein  $\text{R}_{1,2}$  and  $\text{R}_{1,3}$  are independently hydrogen or lower alkyl;

wherein  $\text{R}_{1,4}$  is selected from the group consisting of hydrogen, hydroxyl, nitrile, nitro, nitroso, halogen, lower alkyl, lower alkoxy, lower alkylseleno, lower alkylamino or diloweralkylamino; or  $\text{R}_{1,4}$  and  $\text{R}_{1,5}$  together are  $-\text{CH}_2-$ ,  $-\text{CHX}-$ ,  $-\text{CX}_2-$ , ( $\text{X}$  = halogen, carboxyl or alkoxycarbonyl),  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{Se}-$ ,  $>\text{N}-\text{CN}$ ,  $>\text{NR}_{2,9}$  and  $>\text{NCO}_2\text{R}_{2,9}$ , wherein  $\text{R}_{2,9}$  is hydrogen or lower alkyl;

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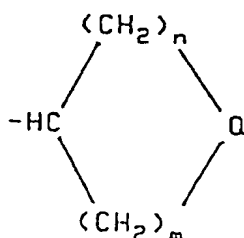
wherein  $R_{1s}$  is selected from the group consisting of hydrogen, hydroxyl, nitro, nitroso, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower alkylseleno, lower alkylamino, di(lower)alkylamino, nitrile, azido, arylseleno,  $AXR_{2,1}$ ,  $A^1-[Y-A^{1,1}]_U-X-R_{2,1}$  or  $R_{1s}$  and  $R_{1s}$  together are  $-CH_2-$ ,  $-CHX-$ ,  $-CX_2-$ , ( $X$  = halogen, carboxyl or alkoxycarbonyl),  $-O-$ ,  $-S-$ ,  $-Se-$ ,  $>N-CN$ ,  $>NR_{2,1}$ , and  $>NCO_2R_{2,1}$ , wherein  $R_{2,1}$  is hydrogen or lower alkyl;

wherein  $R_{1s}$  is selected from the group consisting of hydrogen, nitroso, halogen, lower alkyl, carboxyl, lower alkoxy, lower alkylseleno, lower alkylamino, nitrile, azido, arylseleno, lower alkylseleno, di(lower)alkylamino,  $AXR_{2,1}$ , or  $A^1-[Y-A^{1,1}]_U-X-R_{2,1}$ ,

wherein  $R_{1,(\alpha)}$  is selected from the group consisting of hydrogen, hydroxyl, lower alkyl, halogeno(lower)alkyl,  $AXR_{2,1}$ ,  $A^1-[Y-A^{1,1}]_U-X-R_{2,1}$ ,  $B^1-T-R_{3,0}$ , wherein:

$B^1$  is straight- or branched-chain  $(C_1-C_{12})$ alkylene,  $(C_2-C_{12})$ alkynylene,  $(C_2-C_{12})$ alkenylene;  $T$  is  $-O-$ ,  $-NR_{3,1}$ ,  $-Se-$ ,  $-S-$  or  $S-S$  and  $R_{3,0}$  and  $R_{3,1}$  are independently hydrogen, lower alkyl, or  $R_{3,0}$  and  $R_{3,1}$  together are  $(C_3-C_7)$ cycloalkyl,  $(C_5-C_7)$ cycloalkenyl,  $(C_3-C_7)$ cycloalkyl or  $(C_5-C_7)$ cycloalkenyl having one or more hydrogen atoms replaced by halogen atoms,  $-HC=CHR_{3,2}$ , and  $-C=CR_{3,2}$ , wherein:

$R_{3,2}$  and  $R_{3,2}$  are independently hydrogen, halogen, tri(lower)alkylsilyl, carboxyl, carbonyl, lower alkoxy, nitrile, sulfinyl lower alkyl,  $AXR_{2,1}$ ,  $A^1-[Y-A^{1,1}]_U-X-R_{2,1}$  or a species represented by the formula:

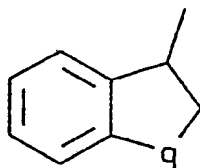


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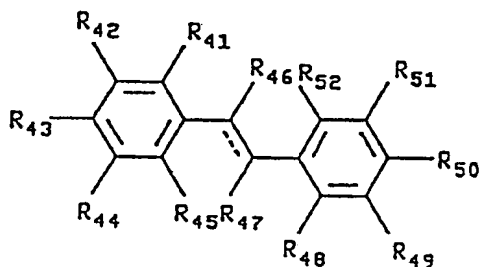
wherein  $n$  and  $m$  are independently 0 to 6 and  $Q$  is  $-\text{Se}-$ ,  $-\text{SiH}_2-$ ,  $-\text{S}-$ ,  $-\text{O}-$  or  $-\text{NR}_{3,4}-$  wherein  $R_{3,4}$  is hydrogen, lower alkyl or  $(\text{C}_1-\text{C}_7)\text{alkanoyl}$ ;  
 or a species represented by the formula:



b

wherein  $q$  is  $-\text{CH}_2-$ ,  $-\text{S}-$ ,  $-\text{O}-$  or  $-\text{NR}_{3,5}-$  wherein  $R_{3,5}$  is hydrogen or lower alkyl;  
 wherein  $R_{1,(\beta)}$  is preferably selected from the group consisting of hydrogen, hydroxyl, halogen, alkoxy,  $(\text{C}_1-\text{C}_7)\text{alkanoyloxy}$ ,  $(\text{C}_3-\text{C}_7)\text{alkenoyloxy}$ ,  $(\text{C}_3-\text{C}_7)\text{alkynoyloxy}$ , cycloalkenyloxy, 1-alkyloxy-alkyloxy, 1-alkyloxy cycloalkyloxy, alkylsilyloxy and a divalent common species formed jointly by  $R_{1,(\alpha)}$  and  $R_{1,(\beta)}$ , said divalent common species being selected from the group consisting of  $=\text{O}$ ,  $=\text{S}$ ,  $=\text{NR}_{3,6}$  or  $=\text{NOR}_{3,6}$  wherein  $R_{3,6}$  is hydrogen or lower alkyl.

An alternative antiestrogen may be represented by the general formula II:



II

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where the dotted lines represent an optional double bond of Z or E configuration;

wherein  $R_{4,1}$ ,  $R_{4,5}$ ,  $R_{4,8}$ , and  $R_{5,2}$  are independently selected from the group consisting of hydrogen, hydroxyl, halogen, lower alkyl, lower alkoxy, alkylsulfonyl lower alkoxy, arylsulfonyl lower alkoxy, lower alkylsilyl, amino, nitro, nitrile and nitroso.

wherein  $R_{4,2}$ ,  $R_{4,4}$ ,  $R_{4,9}$  and  $R_{5,1}$  are independently selected from the group consisting of hydrogen, hydroxyl, halogen, lower alkyl, lower alkoxy, alkylsulfonyl lower alkoxy, arylsulfonyl lower alkoxy, lower alkylsilyl, amino, nitrile, nitro, nitroso, azido, lower alkylamino, dilower alkylamino,  $AXR_{4,1}$ ,  $Y_{4,7}-A^1[Y-A^1]_u-X-R_{4,1}$ ,  $A^1-[Y-A^1]_u-X-R_{4,1}$  wherein:

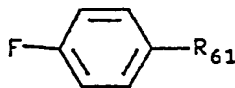
$A$ ,  $A^1$ ,  $A^{11}$ ,  $X$ ,  $Y$  and  $u$  are defined as previously in formule I, and  $Y_{4,7}$  is absent or is selected from the group consisting of carbonyl and carboxyl;

wherein  $R_{4,3}$  and  $R_{5,0}$  are independently selected from the group consisting of hydrogen, hydroxyl, halogen, lower alkyl, methoxy, ethoxy, propoxy, hydroxyethoxy, lower alkoxy, lower alkoxy carbonyloxy, carboxyl, acetoxo, propionyloxy, butyryloxy, oenanthoyloxy, cypionoyloxy, trans-4-n-butyl-cyclohexanecarbonoyloxy,  $(C_1-C_{2,0})$  alkanoyloxy,  $(C_3-C_{2,0})$  alkenoyloxy,  $(C_3-C_{2,0})$  alkynoyloxy,  $(C_7-C_{11})$  aroyloxy and alkylsilyloxy;

wherein  $R_{4,6}$  and  $R_{4,7}$  are independently selected from the group consisting of hydrogen, amino, lower alkylamino, dilower alkyl amino, nitro, nitrile, nitroso, halogen, lower alkyl, lower alkenyl, lower alkynyl, halogeno lower alkyl, halogeno lower alkenyl, halogeno lower alkynyl, alkyl sulfonyl, aryl sulfonyl, a substituted 5- to 7-member heterocyclic ring having at least one heteroatom (selected from oxygen, sulfur, silicon, selenium, nitrogen),  $-(CH_2)_sV$  (wherein  $V$  is nitrile, hydroxyl, azido, nitroso, alkoxy, nitro, thionitrile, halogen, alkyl sulfonyl or aryl sulfonyl and  $s$  is an integer from 1 to 6), a moiety of the formula:

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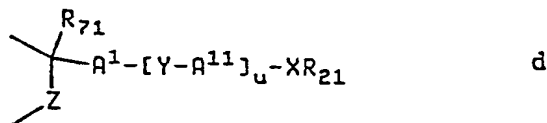
wherein:

F is absent or selected from the group consisting of alkyl, carbonyl or carboxyl, wherein the phenyl ring may be halogenated, wherein  $R_{61}$  is selected from the group consisting of hydrogen, hydroxyl, halogen, lower alkyl, lower alkenyl, lower alkynyl, nitrile, nitro, nitroso or  $X_{46}(CH_2)_nY_{46}$  ( $X_{46}$  being selected from the group consisting of -O-, -S-, -Se-, -SO-, -SO<sub>2</sub>- and -CO-, and  $Y_{46}$  being selected from the group consisting of hydroxyl, amino, monoalkyl amino, dialkyl amino, dimethyl N-oxide, N-aziridyl, guanidino, N-pyrrolidino, N-piperidino, N-methylpiperazino, N-morpholino and alkoxy, and n being an integer from 1 to 6),  $AXR_{11}$ ,  $Y_{47}$ ,  $A^1-[Y-A^{11}]_u-X-R_{21}$ ,  $A^1-[Y-A^{11}]_u-X-R_{21}$  wherein A,  $A^1$ ,  $A^{11}$ , X, Y,  $Y_{47}$  are defined previously for  $R_{42}$ ,  $R_{44}$ ,  $R_4$ , and  $R_{51}$ ;

a species which in combination with another substituent from formula II, forms a moiety selected from the group consisting of -CH<sub>2</sub>-, -CHX-, -CX<sub>2</sub>- (X being halogen, carboxyl or alkoxycarbonyl), -O-, -S-, -Se-, >N-CN, >NR<sub>2</sub>, and >NCO<sub>2</sub>R<sub>2</sub>, ( $R_{21}$  being hydrogen or lower alkyl), lower alkylene,  $-(CH_2)_rO(CH_2)_s-$ ,  $-(CH_2)_rS(CH_2)_s-$ ,  $-(CH_2)_rSe(CH_2)_s-$ ,  $-(CH_2)_rSO(CH_2)_s-$ ,  $-(CH_2)_rSO_2(CH_2)_s-$ ,  $-(CH_2)_rCO(CH_2)_s-$ ,  $-(CH_2)_rNR_{21}(CH_2)_s-$ ,  $-(CH_2)_rSiR_{21}R_{21}(CH_2)_s-$  and  $-(CH_2)_rCR_{21}OR_{21}(CH_2)_s-$  (wherein  $R_{21}$  being hydrogen or lower alkyl, r and s being independent integers from 0 to 3); a moiety of the formula:

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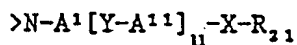
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wherein:

Z is absent or is selected from the group consisting of lower alkylene, halogeno lower alkylene,  $-(\text{CH}_2)_n \text{O}-$ ,  $-(\text{CH}_2)_n \text{S}-$ ,  $-(\text{CH}_2)_n \text{Se}-$ ,  $-(\text{CH}_2)_n \text{SO}-$ ,  $-(\text{CH}_2)_n \text{SO}_2-$ ,  $-(\text{CH}_2)_n \text{CO}-$ ,  $-(\text{CH}_2)_n \text{NR}_{2,1}-$ ,  $-(\text{CH}_2)_n \text{SiR}_{2,1} \text{R}_{2,1}-$  and  $-(\text{CH}_2)_n \text{CR}_{2,1} \text{OR}_{2,1}-$ , n being an integer from 3, and  $R_{71}$  being selected from a group consisting of hydrogen, hydroxyl, halogen, lower alkyl, lower alkoxy and lower alkylsil;

the formula:



wherein:

N is nitrogen atom and  $A^1$ , Y,  $A^{11}$ , u, X and  $R_{2,1}$  are defined as previously.

The inhibitors of sex steroid biosynthesis found useful in the present invention include those compounds which inhibit biosynthesis of sex steroids from precursor steroids of adrenal and/or ovarian origin(s) preferably of both ovarian and adrenal origin. Their action can also be exerted in the peripheral tissues, especially in the breast and the endometrium.

Typical inhibitors of sex steroid biosynthesis include but are not limited to 3-(4-aminophenyl)-3-ethyl-2,6-piperidinedione which is commonly called aminoglutethimide, which is an inhibitor of sex steroid biosynthesis of adrenal but also of ovarian and testicular origin and which is available from Ciba Pharmaceutical Co., Summit N.J. under the

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trade name Cytadren, or ketoconazole, an effective testicular but also adrenal sex steroid biosynthesis, an inhibitor which is available from Janssen Pharmaceuticals, Piscataway, N.J., under the trade name Nizoral.

When an inhibitor of adrenal sex steroid biosynthesis, e.g., amino-glutethimide is administered, cortisol biosynthesis is blocked. Accordingly, a glucocorticoid, e.g. hydrocortisone, is administered in physiological amounts sufficient to maintain normal glucocorticoid activity. Synthetic glucocorticoids can also be used.

The inhibitor of sex steroid formation could also be one or a combination of the above-mentioned steroid and non steroid compounds bearing one or more of the alkyl substituents described above.

The inhibitor of sex steroid formation could also be an inhibitor of aromatase activity (4-OH-androstenedione and FCE 34304, as examples) or of  $3\beta$ -hydroxysteroid,  $\Delta^5$ - $\Delta^4$ -isomerase activity such as Trilostane, Epostane or 4-MA, as examples. Of particular interest, 16-methylene estrone and 16-methylene estradiol act as specific inhibitors of  $17\beta$ -estradiol dehydrogenase (Thomas et al., J. Biol. Chem. 258: 11500-11504, 1983).

Referring to synthesis scheme I below, a preferred antiestrogen which may also act as an inhibitor of sex hormone formation (e.g. inhibitor of estrogen formation) may be prepared as follows:

N-butyl, N-methyl-11-(16 $\alpha$ -chloro-3',17' $\beta$ -dihydroxy-estra-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 139", Scheme 1)

N-butyl, N-methyl-11-(3',17'-diacetoxy-estra-1',3',5'(10'), 16'-tetraen-7' $\alpha$ -yl) undecanamide (3)

To 11-(3-benzoyloxy-17-oxo-estra-1,3,5(10)-trien-7 $\alpha$ -yl) undecanoic acid (1) (3.94 g, 7.22 mmol), prepared as described (Bucourt et al., J. Biol. Chem. 253: 8221-8228, 1978), dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (100 ml)

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and cooled at  $-10^{\circ}\text{C}$  was added tributylamine (2.18 ml, 9.15 mmol) and isobutylchloroformate (1.30 ml, 10.0 mmol). The solution was stirred during 35 min. and N-methylbutylamine (13 ml, 109.7 mmol) was added. The mixture was warmed to room temperature and stirred during 1 h. Afterward,  $\text{CH}_2\text{Cl}_2$  was added and the organic phase was washed with 1N HCl, water, saturated sodium bicarbonate solution and finally with water, dried with anhydrous  $\text{MgSO}_4$  and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel. Elution with mixture of EtOAc/hexane (1.5:8.5 v/v) yielded N-butyl, N-methyl-11-(3'-benzoyloxy-17'-oxo-estra-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide (4.25 g, 96%) as colorless oil; IR  $\nu$  (neat) 1750, 1725 and 1640  $\text{cm}^{-1}$ . The above described benzoyloxy amide (341 mg, 0.54 mmol) was dissolved in methanol (10 ml) and cooled at  $0^{\circ}\text{C}$ . Following this 2N NaOH (5 ml) was added and the mixture was stirred during 60 min. at  $0^{\circ}\text{C}$ . The solution was neutralized with 1N HCl and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic phase was dried with anhydrous  $\text{MgSO}_4$  and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel. Elution with mixture of EtOAc/hexane (3:7 v/v) yielded N-butyl, N-methyl-11-(3'-hydroxy-17'-oxo-estra-1',3',4'(10)-trien-7' $\alpha$ -yl) undecanamide (2) (284 mg, 97%) as colorless oil;  $^1\text{H-NMR}$   $\delta$  ( $\text{CDCl}_3$ ) 0.91 (s, 3H, 18'- $\text{CH}_3$ ), 2.76 app(d, 1H, J=16.3 Hz, part of ABX system, 6'-H) 2.96 and 2.98 (2s, 3H N- $\text{CH}_3$ ), 3.27 and 3.38 (2t<sub>app</sub>, 2H, J=7.5 Hz, N- $\text{CH}_2$ -), 6.63 (broad s, 1H, 4'-H), 6.70 (broad d, 1H, J=8.5 Hz, 2'-H), 7.12 (d, 1H, J=8.4 Hz, 1'-H); IR  $\nu$  (neat) 3270, 1730, 1615  $\text{cm}^{-1}$ ; MS m/e 523 ( $\text{M}^+$ , 100%), 508 ( $\text{M}^+ - \text{CH}_3$ , 32%), 142 ( $\text{C}_2\text{H}_5\text{CON}(\text{CH}_3)\text{C}_6\text{H}_5^+$ , 47%). The ketone amide 2 (163 mg, 0.50 mmol) was dissolved in isoprenyl acetate (10 ml). p-Toluenesulfonic acid (44 mg) was then added and the solution was distilled to about two-thirds of the original volume in 7

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hrs and was then stirred at reflux for 12 hrs. Afterwards, the solution was cooled with an ice-water bath and extracted with 50 ml of cooled ether. The ether was washed with a cooled saturated sodium bicarbonate and water. The organic phase was dried with anhydrous  $\text{MgSO}_4$  and the solvent was removed under reduced pressure. The residue was filtered through alumina (15mm x 50 mm alumina Woehlm neutral, activity II) using a mixture of benzene-diethyl ether (3:7 v/v) as eluant. The solvent was removed under reduced pressure and, the residue was purified by flash chromatography on silica gel. Elution with mixture of EtOAc/hexane (1:4 v/v) yielded the N-butyl, N-methyl-11-(3',17'-diacetoxy-estra-1',3',5'(10'), 16'-tetraen-7' $\alpha$ -yl) undecanamide (3) (244 mg, 80%) as colorless oil;  $^1\text{H-NMR}$   $\delta$  ( $\text{CDCl}_3$ ) 0.92 (s, 3H, 18'- $\text{CH}_3$ ), 0.92 and 0.95 (2t, 3H,  $\text{J}=7.0$  Hz,  $\text{N}(\text{CH}_2)_3\text{CH}_3$ ), 2.18 (s, 3H, 17'- $\text{OCOCH}_3$ ), 2.28 (s, 3H, 3'- $\text{OCOCH}_3$ ), 2.76 app (d, 1H,  $\text{J}=16.1$  Hz, part of ABX system, 6'-H), 2.90 and 2.96 (2s, 3H, N- $\text{CH}_3$ ), 3.26 and 3.35 (2t<sub>app</sub>, 2H,  $\text{J}=7.6$  Hz, N- $\text{CH}_2$ -), 5.52 (m, 1H, 16'-H), 6.80 (broad s, 1H, 4'-H), 6.85 (dd, 1H,  $\text{J}_1=9.1$  Hz and  $\text{J}_2=3.0$  Hz, 2'-H), 7.27 (d, 1H,  $\text{J}=9.1$  Hz, 1'-H); IR  $\nu$  (neat) 1750, 1635, 1200  $\text{cm}^{-1}$ ; MS m/e 607 ( $\text{M}^+$ , 2%), 565 ( $\text{M}^+-\text{COCH}_3$ , 100%), 550 ( $\text{M}^+-\text{COCH}_2\text{CH}_3$ , 13%), 523 ( $\text{M}^+-2\text{COCH}_3$ , 45%), 142 ( $\text{C}_4\text{H}_9\text{CON}(\text{CH}_3)\text{C}_4\text{H}_9^+$ , 55%), 129 ( $\text{C}_4\text{H}_9(\text{CH}_3)\text{NCOCH}_3^+$ , 38%), 114 ( $\text{C}_4\text{H}_9(\text{CH}_3)\text{NCO}^+$ , 60%), 86 ( $\text{C}_4\text{H}_9(\text{CH}_3)\text{N}^+$ , 25%); EXACT MASS calcd for  $\text{C}_{33}\text{H}_{57}\text{O}_5\text{N}$  607.4239, found 607.4234.

The N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3'acetoxy-17'-oxo-estra-1',3',4'(10')-triene-7' $\alpha$ -yl) undecanamide (4)

To diacetate amide 3, dissolved in 5 ml of acetone, was added a solution of sodium acetate (2.6 equivalents) in acetic acid and water (1:11.3 v/v) and then, was treated with tertbutyl hypochlorite (1 eq.) prepared from t-butanol (4 ml) and Javel water (Javex 6.1%, 50 ml). The clear solution was warmed to 55°C and stirred for 1 h. Afterwards, the

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solvent was evaporated to dryness. The residue was dissolved in ether (100 ml) and water was added (20 ml). The organic phase was washed with water, dried with anhydrous  $\text{MgSO}_4$  and evaporated to dryness. The residue was purified by chromatography on silica gel carried out with mixture of EtOAc/hexane (3:7 v/v) to give the N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3'acetoxy-17'-oxo-estra-1',3',4'(10')-trien-7' $\alpha$ -yl) undecanamide (4) (115 mg, 89%) as colorless oil;  $^1\text{H-NMR}$   $\delta$  ( $\text{CDCl}_3$ ) 0.92 and 0.95 (2t, 3H,  $J=7.0$  Hz,  $\text{N}(\text{CH}_2)_2\text{CH}_3$ ), 0.96 (s, 3H, 18'- $\text{CH}_3$ ), 2.28 (s, 3H, 3'- $\text{OCOCH}_3$ ), 2.80 app (d, 1H,  $J=16.6$  Hz, part of ABX system, 6'-H) 2.90 and 2.96 (2s, 3H,  $\text{N-CH}_3$ ), 3.24 and 3.35 (2t<sub>app</sub>, 2H,  $J=7.4$  Hz,  $-\text{N-CH}_2-$ ), 4.46 (d, 1H,  $J=6.6$  Hz, 16' $\beta$ -H), 6.82 (broad s, 1H, 4'-H), 6.86 (dd, 1H,  $J=9.1$  Hz and  $J_2=2.6$  Hz, 2'-H), 7.29 (d, 1H,  $J=9.1$  Hz, 1'-H); IR (neat) 1750, 1640, 1205  $\text{cm}^{-1}$ ; MS  $m/e$  601, 599 ( $\text{M}^+$ , 24%, 68%), 142 ( $\text{C}_2\text{H}_4\text{CON}(\text{CH}_2)_2\text{C}_4\text{H}_9^+$ , 100%), 114 ( $\text{C}_4\text{H}_9(\text{CH}_2)_2\text{NCO}^+$ , 93%).

N-butyl, N-methyl-11-(16 $\alpha$ -chloro-3',17' $\beta$ -dihydroxy-estra-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 139")

A stirred solution of haloketone amide 4 in anhydrous tetrahydrofuran (THF) (10 ml) under argon was chilled to  $-70^\circ\text{C}$  with 2-propanol/dry ice bath to  $-70^\circ\text{C}$  with 2-propanol/dry ice bath. A solution of 1.0 M of lithium aluminium hydride (2 eq.) was then added dropwise. After 30 min, the reaction was allowed to return slowly at  $0^\circ\text{C}$  for 5 min, then was quenched by the dropwise addition of a mixture of THF-EtOAc (5 ml) (1:1 v/v) and acidified at pH  $\sim 4$  with (10%) HCl. The mixture was stirring for 5 min. at room temperature and then extracted with EtOAc. The organic phase was washed with water, dried on anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated

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under reduced pressure. The residue included two important antiestrogens which were separated by chromatography on silica gel and eluted with a mixture of EtOAc/hexane (4:6 v/v):

N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\alpha$ -dihydroxy-estra-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 170") (15 mg, 29%) as colorless oil; analytical sample was obtained by HPLC purification;  $^1\text{H-NMR}$   $\delta$  ( $\text{CDCl}_3$ , 400 MHz) 0.79 (s, 3H, 18'- $\text{CH}_3$ ), 0.93 and 0.96 (2t, 3H,  $J=7.3$  Hz,  $\text{N}(\text{CH}_2)_3\text{CH}_3$ ), 2.80 (2H,  $J_{6,6}=17.1$  Hz and  $J_{6,7}=4.5$  Hz,  $\Delta\delta=24.34$  (Hz, system ABX, 6'-H), 2.94 and 2.99 (2s, 3H,  $\text{N-CH}_3$ ), 3.26 (dd,  $J_1=7.6$  Hz and  $J_2=7.4$  Hz) and 3.32-3.43 (m)  $-\text{[2H, -N-CH}_2\text{-]}$ , 3.71 (d, 1H,  $J=4.5$  Hz, 17' $\beta$ -H), 4.63 (ddd, 1H,  $J_{15,15}=10.2$  Hz,  $J_{16,17}=4.5$  Hz and  $J_{16,15}=3.9$  Hz, 16' $\beta$ -H), 6.50 (d, 1H,  $J=24$  Hz, 3'-OH), 6.60 (d, 1H,  $J=2.5$  Hz, 4'-H), 6.66 (dd, 1H,  $J_1=8.4$  Hz and  $J_2=2.5$  Hz, 2'-H), 7.14 (d, 1H,  $J=8.5$  Hz, 1'-H); IR  $\nu$  (neat) 3300, 1615, 1495  $\text{cm}^{-1}$ ; MS  $m/e$  561, 559 ( $\text{M}^+$ , 40%, 100%), 523 ( $\text{M}^+-\text{HCl}$ , 20%), 142 ( $\text{C}_2\text{H}_4\text{CON}(\text{CH}_3)\text{C}_4\text{H}_9^+$ , 44%), 114 ( $\text{C}_4\text{H}_9(\text{CH}_3)\text{CNO}^+$ , 37%); Exact mass calculated for  $\text{C}_{34}\text{H}_{50}\text{O}_2\text{N}^{35}\text{Cl}$  559.3785, found 559.3821;

- and -

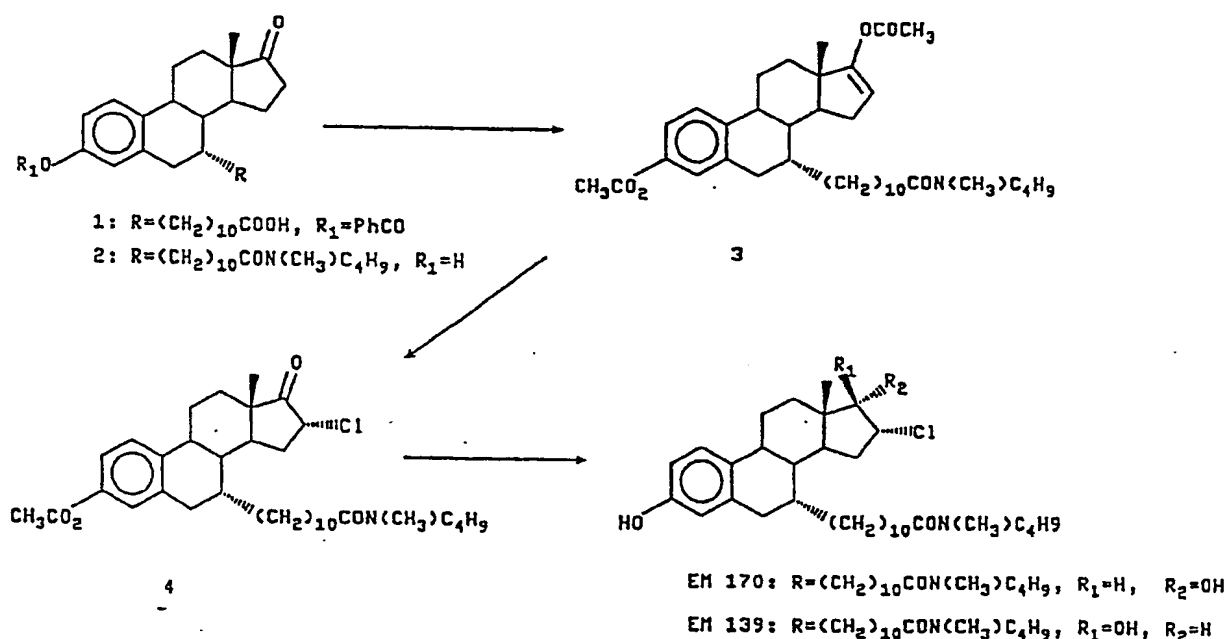
-N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\beta$ -dihydroxy-estra-1'3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 139") (25 mg, 55%) as a colorless oil; analytical sample was obtained by HPLC purification;  $^1\text{H-NMR}$   $\delta$  ( $\text{CDCl}_3$ , 400 MHz), 0.81 (s, 3H, 18'- $\text{CH}_3$ ), 0.93 and 0.96 (2t, 3H,  $J=7.3$  Hz,  $(\text{CH}_2)_3\text{CH}_3$ ), 2.78 (2H,  $J_{6,6}=16.2$  Hz and  $J_{6,7}=4.5$  Hz,  $\Delta\delta=24.34$  Hz, system ABX, 6'-H), 2.94 and 2.99 (2s, 3H,  $\text{N-CH}_3$ ), 3.27 (dd,  $J_1=7.6$  Hz and  $J_2=7.5$  Hz) and 3.31-3.45 (m)  $[\text{2H, -N-CH}_2\text{-}]$ , 3.86 (dd, 1H,  $J_{17,17-\text{OH}}=3.4$  Hz and  $J_{17,16}=5.9$  Hz, 17' $\alpha$ -H), 4.11 (ddd, 1H,  $J_{16,15}=10.8$  Hz,  $J_{16,17}=5.9$  Hz and

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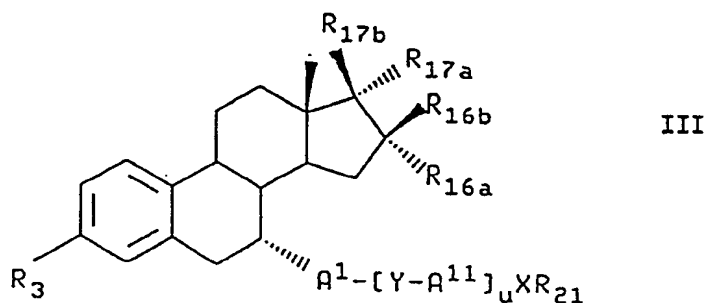
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$J_{16,15}=2.5$  Hz,  $16'\beta$ -H), 6.56 (d, 1H,  $J=19.7$  Hz,  $3'$ -OH), 6.61 (d, 1H,  $J=2.5$  Hz,  $4'$ -H), 6.66 (dd, 1H,  $J_1=8.4$  Hz and  $J_2=2.6$  Hz,  $2'$ -H), 7.13 (d, 1H,  $J=8.4$  Hz,  $1'$ -H); IR  $\nu$  (neat) 3320, 1615, 1490  $\text{cm}^{-1}$ ; MS  $m/e$  561, 559 ( $M^+$ , 38%, 100%), 523 ( $M^+-\text{HCl}$ , 16%), 142 ( $\text{C}_2\text{H}_4\text{CON}(\text{CH}_3)\text{C}_4\text{H}_9^+$ , 80%), 114 ( $\text{C}_4\text{H}_9(\text{CH}_3)\text{NCO}^+$ , 76%); Exact mass calculated for  $\text{C}_{34}\text{H}_{50}\text{O}_3\text{N}^+\text{Cl}$  559.3785, found 559.3825.

Scheme 1



A preferred inhibitor of  $17\beta$ -estradiol dehydrogenase possesses moreover an antiestrogenic activity and is represented, for example, by the compound of the formula III:



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wherein  $R_1$  is selected from the group consisting of hydroxyl, halogen, lower alkoxy, methoxy, ethoxy, propoxy, hydroxyethoxy,  $(C_1-C_{10})$ alkanoyloxy, acetoxy, propionyloxy, butyryloxy, oenanthoyloxy, cypionoyloxy, trans-4-n-butyl-cyclohexanecarbonoyloxy, lower alkoxy carbonyloxy, carboxy,  $(C_1-C_{10})$ alkenoyloxy,  $(C_1-C_{10})$ alkynoyloxy,  $(C_1-C_{10})$ aroyloxy;

wherein  $R_{17}(\alpha)$  is selected from the group consisting of hydrogen and hydroxyl;

wherein  $R_{16}(\alpha)$  is a halogen, preferably chlorine, fluorine, or bromine;

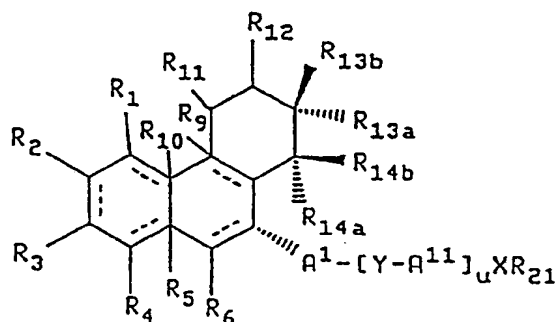
$R_{16}(\beta)$  is preferably hydrogen, or  $R_{16}(\alpha)$  and  $R_{16}(\beta)$  together form  $=C_2$ ;

wherein  $G_1$  is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkenyl, lower alkynyl, nitrile, alkoxycarbonyl, alkylcarbonyl and carboxyl;

wherein  $R_{17}(\beta)$  is selected from the group consisting of hydrogen, hydroxyl,  $(C_1-C_7)$ alkanoyloxy,  $(C_1-C_7)$ alkenoyloxy,  $(C_1-C_7)$ alkynoyloxy, cycloalkenoyloxy, 1-alkyloxy-alkyloxy, 1-alkyloxy cycloalkyloxy, alkylsilyloxy and a divalent common species formed jointly by  $R_{17}(\alpha)$  and  $R_{17}(\beta)$ , said divalent common species being selected from the group consisting of  $=O$ ,  $=S$ ,  $NR_{36}$  or  $NOR_{36}$ , wherein  $R_{36}$  is hydrogen or lower alkyl;

wherein  $A^1$ ,  $A^{11}$ ,  $Y$ ,  $X$ ,  $R_{21}$  and  $u$  are defined previously in the formula I;

And/or by 16,17-secosteroid derivative of the molecular formula:



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wherein the dotted lines represent optional double bonds, wherein the A-ring is optionally aromatic;

wherein  $R_1$ ,  $R_2$  and  $R_3$  are independently selected from the group consisting of hydrogen, hydroxyl, halogen, lower alkyl, lower alkoxy, lower alkylsilyl, amino and nitro;

wherein  $R_4$  is selected from the group consisting of hydroxyl, halogen, lower alkoxy,  $(C_2-C_{10})$ alkanoyloxy,  $(C_3-C_{10})$ alkenoyloxy,  $(C_3-C_{10})$ alkynoyloxy,  $(C_7-C_{10})$ aroyloxy, lower alkoxycarbonyloxy or a divalent common species formed jointly by  $R_{3(\alpha)}$  and  $R_{3(\beta)}$  said divalent common species being selected from the group consisting of  $=O$ ,  $=S$ ,  $=NR_{3,6}$  or  $=NOR_{3,6}$  wherein  $R_{3,6}$  is hydrogen or lower alkyl;

wherein  $R_5$  and  $R_{10}$  are absent or selected from the group consisting of hydrogen or lower alkyl;

wherein  $R_6$  is selected from the group consisting of hydrogen, halogen, lower alkyl, amino or nitrile;

wherein  $R_{11}$  is selected from the group consisting of hydrogen, lower alkyl, lower alkynyl,  $(C_6-C_{10})$ aryl, a substituted 5- to 7-member heterocyclic ring having at least an heteroatom (selected from oxygen, sulfur, silicon, selenium and nitrogen),  $(CH_2)_sW$  (wherein W is nitrile, hydroxyl, azido, nitroso, nitro, thionitrile, halogen, alkylsulfonyl or arylsulfonyl, and s is an integer from 1 to 6),  $OR_{2,6}$  (wherein  $R_{2,6}$  is hydrogen, lower alkyl or  $(C_6-C_{10})$ aryl),  $DR_{2,7}$  (wherein D is  $-Se-$ ,  $-NR_{2,8}-$ ,  $-S-$  or  $-O-$ , and  $R_{2,7}$  is hydrogen or lower alkyl),  $=O$ ,  $=S$ ,  $=Se$ ,  $=NR_{2,8}$  and  $=NOR_{2,8}$  (wherein  $R_{2,8}$  is hydrogen or lower alkyl);

wherein  $R_{12}$  and  $R_{13(\beta)}$  are hydrogen or lower alkyl;

wherein  $R_{13(\alpha)}$  is selected from the group consisting of 1-oxo-2-propynyl,

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1-hydroxy-2-propynyl, carboxyl, alkoxycarbonyl and alkylcarbonyl;  
wherein  $R_{1,2}(\alpha)$  and  $R_{1,2}(\beta)$  are selected from the group consisting of  
hydrogen, hydroxyl, lower alkyl, lower alkenyl, lower alkynyl and  
halogeno analogs of the foregoing;

wherein  $A^1$ ,  $A^{11}$ , Y, n, X,  $R_{2,1}$  are defined as previously in the formula 1.

A preferred inhibitor of prolactin secretion is bromocryptine, e.g. Parlodel (available from Sandoz, Bale, Switzerland). A preferred inhibitor of growth hormone secretion is a somatostatin analogue, e.g. Sandostatin (available from Sandoz, Bale, Switzerland). A preferred inhibitor of ACTH secretion is hydrocortisone acetate, e.g. Solucortef. (available from Upjohn).

In this invention, the LHRH agonist or antagonist, antiestrogen, androgen, and, where applicable, the progestin, the inhibitor of steroid biosynthesis (hydrocortisone) and the inhibitor of prolactin and/or growth hormone and/or ACTH secretion are administered as pharmaceutical compositions via topical, parenteral or oral means. The LHRH agonist or antagonist is administered parenterally, i.e., intramuscularly, subcutaneously or intravenously by injection or infusion by nasal drops or by suppository, where applicable intra-vaginally. The LHRH agonist or antagonist may also be microencapsulated in or attached to a biocompatible, biodegradable polymer, e.g., poly(d,l-lactide-co-glycolide) and subcutaneously or intramuscularly injected by a technique called subcutaneous or intramuscular depot to provide continuous, slow release of the LHRH agonist or antagonist over a period of 30 days or longer. The most preferred route of administration of the LHRH agonist or antagonist is subcutaneous depot injection. Preferably the antiestrogen will be administered oral-

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ly. Preferably, the inhibitors of sex steroid biosynthesis such as aminoglutethimide and ketoconazole, the androgen and progestin, as well as the inhibitor of prolactin, growth hormone and ACTH secretion, when used, are administered orally. The antiestrogen, androgen, progestin and inhibitor of sex steroid formation can also be administered in a slow release formulation, e.g. poly(d,l-lactide-coglycolide) or as implants.

The amount of each component administered is determined by the attending clinicians taking into consideration the etiology and severity of the disease, the patient's condition and age, the potency of each component and other factors. In the combination therapy of breast and endometrial cancer, according to this invention, the following dosage ranges are suitable.

The LHRH agonist or antagonist is generally administered at from about 10 to 5000 µg per day with contemplated dosage ranges of about 10 to 1500 µg per day and about 250 (preferably 200 µg to 500 µg per day) for the LHRH agonist and to about 50 to 5000 µg per day for the LHRH antagonist being preferred.

In the most preferred embodiment of this invention, the LHRH agonist or antagonist is administered subcutaneously in a daily dose of 500 µg for the first 30 days and thereafter subcutaneously in a daily dose of 250 µg regardless of the patients' body weight. When the LHRH agonist or antagonist is administered, once every 30-day period is used, with a dose of 750 to 15,000 µg per 30-day period being preferred. Similar daily delivery doses are used for longer-term controlled release formulations.

The androgen and progestin compositions are generally administered in a dosage range of about 0.10 to 40 mg/kg (body weight) per day with 45 mg per day in three equally divided doses being preferred.

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The aminoglutethimide compositions (when used) are administered initially in a dosage of 250 mg given at 8-hour intervals and the dosage may be increased in increments of 250 mg daily up to a total daily dose of 2 grams.

The ketoconazole compositions (when used) are administered orally in a dose of 250 mg given at 8-hour intervals and may be increased to a daily dose of 2 grams.

Other inhibitors of sex steroid biosynthesis are preferably administered in dosages ranging from about 0.1 to 40 mg/kg per day with 45 mg per day in three equally divided doses being preferred.

The antiestrogen compositions are administered in a dosage range of about 0.05 to 25 mg/kg body weight per day, with 10 mg, especially 20 mg, in two equally divided doses being preferred.

The inhibitor of prolactin secretion, bromocriptine, being the example, is administered at the dose of 2 mg once or twice daily. The inhibitor of growth hormone secretion, the somatostatin analog, sandostatin, being an example, is administered subcutaneously at the dose of 100 to 1000 µg per day in these equally divided doses.

The glucocorticoid (also inhibitor of ACTH secretion), especially hydrocortisone compositions (when used), are administered orally in a dosage range of about 0.1 to 20 mg/kg body weight per day. Preferably, the hydrocortisone is administered orally at the dose of about 10 mg in the morning and about 5 mg doses in the afternoon and in the evening.

The LHRH agonist or antagonist, antiestrogen, androgen, progestin and inhibitor of sex steroid biosynthesis as well as the inhibitor of prolactin, growth hormone and ACTH secretion each may be administered separately or when the modes of administration are the same, all or at least two of them may be administered in the same composition, but in any

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case the preferred ratio of LHRH agonist to antiestrogen, to androgen (when used), to progestin (when used), to inhibitor of sex steroid biosynthesis (when used) administered daily will be about 250 µg of LHRH agonist to about 45 mg of androgen, about 45 mg of progestin, about 15 mg, of antiestrogen, to about 45 mg of inhibitor of sex steroid biosynthesis at about 750 mg of inhibitor of adrenal steroid secretion.

In the therapy of breast and endometrial cancer, combining the administration of an LHRH agonist or antagonist, an antiestrogen, an androgen, and a progestin, the dosages preferable are as follows: the LHRH agonist or antagonist is generally administered at from about 10 to 2000 µg per day, with contemplated dosage ranges of 10 to 500 µg per day, 50-250 µg per day and 250 to 500 µg per day being preferred. In the most preferred embodiment of this aspect of this invention, the LHRH agonist or antagonist is administered subcutaneously in a daily dose of 500 µg for the first 30 days and thereafter subcutaneously in a daily dose of 250 µg regardless of the patients' body weight. When the LHRH agonist or antagonist is administered, once every 30-day period, by intramuscular or subcutaneous depot injection, a dose from about 300 to 60000 (occasionally 15000) µg per 30-day period is used, with a dose of 750 to 6000 µg per 30-day period being preferred. The androgen and progestin compositions are generally administered in a dosage range of about 0.10 to 40 mg/kg (body weight) per day with 45 especially 75 mg per day in three equally divided doses being preferred. The antiestrogen and inhibitor of sex steroid formation compositions are administered in a dosage range of about 0.1 to 25 mg/kg body weight per day, with 10 mg in three, preferably with 20 mg in two, equally divided doses being preferred. The aminoglutethimide compositions when used are administered initially in a dosage of 250 mg given at preferably 8-hour intervals and the dosage may be increased

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in increments of 250 mg daily up to a total daily dose of 2 grams. The ketoconazole compositions when used are administered orally in a dose of 250 mg twice daily and may be increased to 200 mg, four times a day.

The LHRH agonist or antagonist, antiestrogen, androgen, progestin and inhibitor of sex steroid formation, each may be administered separately or when the modes of administration are the same, all or two or three of them may be administered in the same composition, but in any case the preferred ratio of LHRH agonist to androgen (or progestin) to antiestrogen administered daily will be about 250 µg of LHRH agonist to about 45 mg of androgen and progestin to preferably 20 mg of antiestrogen.

In the therapy of breast and endometrial cancer, according to this invention, it is preferred that the LHRH agonist is [D-Trp<sup>6</sup>, des-Gly-NH<sub>2</sub>,<sup>10</sup>]LHRH ethylamide be administered subcutaneously in single daily dose of 500 µg for the first thirty (30) days of treatment and thereafter in a single daily dose of 25 µg; the androgen is MPA which is administered orally in three equally divided daily doses of 15 mg each; and the inhibitor of sex steroid biosynthesis is ketoconazole and/or aminoglutethimide, each of which is administered orally in three equally divided doses of 250 mg every 8 hours; and the hydrocortisone (if used) is administered orally at a dose of about 10 mg in the morning and two equally divided doses of about 5 mg, 8 and 16 hours thereafter; and the antiestrogen is (Z)-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethylamine (Tamoxifen) which is administered orally in two equally divided doses of about 10 mg every 12 hours.

In the combination therapy of breast and endometrial cancer according to this invention, the administration of the antiestrogen, androgen, progestin, inhibitor(s) of steroid biosynthesis, glucocorticoid and LHRH

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agonist or LHRH antagonist can be started in any order of sequence. Preferably, the administration of the androgen and antiestrogen is started before (preferably two to four hours before) the administration of the LHRH agonist or LHRH antagonist is started. Preferably, the administration of the inhibitor(s) of sex steroid biosynthesis is started on the same day as the administration of the LHRH agonist or LHRH antagonist. However, the attending clinician may elect to start administration of the LHRH agonist or antagonist simultaneously with the androgen, progestin and inhibitor of sex steroid formation.

When patients whose ovaries have already been surgically removed are treated according to this invention, the administration and dosage of the androgen and the other components of the therapy (except the LHRH agonist or antagonist which is not used) are the same as indicated for the therapy in which the LHRH agonist or antagonist is used.

The LHRH agonists or antagonists useful in the present invention are typically amorphous solids which are freely soluble in water or dilute acids, e.g., HCl, H<sub>2</sub>SO<sub>4</sub>, citric, acetic, mandelic or fumaric. The LHRH agonist or antagonist for subcutaneous injection is supplied in vials containing 5 ml of sterile solution with the LHRH agonist or antagonist at a concentration of about 1.0 mg/ml.

A typical pharmaceutical composition of the LHRH agonist or antagonist includes the LHRH agonist or antagonist or a pharmaceutically acceptable acid salt thereof, benzyl alcohol, a phosphate buffer (pH 6.0-6.5) and sterile water.

The LHRH agonist or antagonist for intramuscular or subcutaneous depot injection may be microencapsulated in a biocompatible, biodegradable polymer, e.g., poly (d,l-lactide-co-glycolide) by a phase separation process or formed into a pellet. The microspheres may then be suspended

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in a carrier to provide an injectable preparation or the depot may be injected in the form of a pellet. See also European patent application EPA No. 58,481 published Aug. 25, 1982 for solid compositions for subdermal injection or implantation or liquid formulations for intramuscular or subcutaneous injections containing biocompatible, biodegradable polymers such as lactide-glycolide copolymer and an LHRH agonist, e.g. D-Ser-t-BuO<sup>6</sup>, Azgly<sup>10</sup>-LHRH. These formulations permit controlled release of the peptide.

The inhibitors of sex steroid biosynthesis, e.g., aminoglutethimide and ketoconazole and the glucocorticoid, e.g., hydrocortisone (when used) are typically compounded in customary ways for oral administration, e.g., in tablets, capsules and the like.

The androgen and progestin useful in the present invention are typically formulated with conventional pharmaceutical excipients, e.g., spray dried lactose and magnesium stearate into tablets or capsules for oral administration. The antiestrogens, when used with the invention, are typically compounded in customary ways for oral administration, e.g., in capsules, tablets, as dragees or even in liquid form, e.g., suspensions or syrups. One or more of the active substances, with or without additional types of active agents, can be worked into tablets or dragee cores by being mixed with solid, pulverulent carrier substances, such as sodium citrate, calcium carbonate or dicalcium phosphate, and binders such as polyvinyl pyrrolidone, gelatin or cellulose derivatives, possibly by adding also lubricants such as magnesium stearate, sodium lauryl sulfate, "Carbowax" or polyethylene glycols. Of course, taste-improving substances can be added in the case of oral administration forms.

The therapeutically active antiestrogen compound should be present in a concentration of about 0.5-90% by weight of the total mixture, i.e.,

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in amounts that are sufficient for maintaining the above-mentioned dosage range.

As further forms, one can use plug capsules, e.g., of hard gelatin, as well as closed soft-gelatin capsules comprising a softener or plasticizer, e.g. glycerine. The plug capsules contain the active substance preferably in the form of granulate, e.g., in mixture with fillers, such as lactose, saccharose, mannitol, starches, such as potato starch or amylopectin, cellulose derivatives or highly-dispersed silicic acids. In soft-gelatin capsules, the active substance is preferably dissolved or suspended in suitable liquids, such as vegetable oils or liquid polyethylene glycols.

In place of oral administration, the active compounds may be administered parenterally. In such case, one can use a solution of the active substance, e.g., in sesame oil or olive oil. One or more of the active substances (androgen, antiestrogen, progestin and/or inhibitor of sex steroid formation) can be microencapsulated in or attached to a biocompatible, biodegradable polymer, e.g. poly(d,l-lactide-co-glycolide) and subcutaneously or intramuscularly injected by a technique called subcutaneous or intramuscular depot to provide continuous slow release of the compound(s) for a period of 2 weeks or longer.

The invention also provides kits or single packages combining the pharmaceutical compositions useful for the combination treatment of breast and endometrial cancer discussed above. The kits or packages may also contain instructions to use the pharmaceutical compositions in accordance with the present invention. This aspect of the invention is exemplified by the following discussions: for the treatment of breast or endometrial cancer, a four-component kit provides an antiestrogen, an androgen and an inhibitor of sex steroid formation oral pharmaceutical

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compositions and an LHRH agonist or LHRH antagonist parenteral composition while a three-component kit could be an antiestrogen, an androgen oral pharmaceutical composition or the oral compositions of an antiestrogen and an inhibitor of sex steroid biosynthesis with the LHRH agonist or LHRH antagonist parenteral composition.

Following the above treatment using the described regimen, tumor growth and bone metastases of breast and endometrial cancer are inhibited and in some instances complete remission may occur.

The terms and descriptions used herein are preferred embodiments set forth by way of illustration only, and are not intended as limitations on the many variations which those of skill the art will recognize to be possible in practicing the present invention as defined by the following claims.

What is claimed is:

1. A method of treating breast or endometrial cancer in a warm-blooded animal wherein said method comprises inhibiting the ovarian hormonal secretions of said animal and administering to said animal therapeutically effective amounts of an antiestrogen and at least one compound selected from the group consisting of an androgen, a progestin, an inhibitor of sex steroid formation, an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.
2. The method of claim 1 wherein ovarian secretions are inhibited by removal of the ovaries.
3. The method of claim 1 wherein said secretions are inhibited by administering a secretion inhibiting amount of an ovarian secretion in-

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hibitor selected from the group consisting of an LHRH agonist and an LHRH antagonist.

4. The method of claim 3 wherein said ovarian secretion inhibitor is administered together with a pharmaceutically acceptable carrier.
5. The method of claim 4 wherein said ovarian secretion inhibitor is administered parenterally together with a pharmaceutically acceptable parenteral carrier.
6. The method of claim 1 wherein at least one compound selected from the group consisting of an androgen, an antiestrogen, a progestin, an inhibitor of sex steroid formation, an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion is administered orally, together with a pharmaceutically acceptable oral carrier.
7. The method of claim 1 wherein at least one compound selected from the group consisting of an androgen, an antiestrogen, a progestin, an inhibitor of sex steroid formation, an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion is administered parenterally, together with a pharmaceutically acceptable parenteral carrier.
8. The method of claim 3 wherein the LHRH agonist is a polypeptide represented by the formula: L-pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-X-Y-L-arginyl-L-prolyl-Z, wherein X is selected from the group consisting of D-tryptophyl, D-leucyl, D-alanyl, 3-(12-naphthyl)-D-alanyl, O-tert-butyl-D-seryl, D-tyrosyl, D-lysyl-D-phenylalanyl and N-methyl-D-alanyl, wherein Y is selected from the group consisting of L-leucyl, D-leucyl and D-alanyl, and wherein Z

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is selected from the group consisting of glycy1-NHR<sub>1</sub> and NHR<sub>1</sub> (wherein R<sub>1</sub> is H, lower alkyl or lower haloalkyl).

9. The method of claim 1 wherein the antiestrogen is (Z)-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine.
10. The method of claim 1 wherein said inhibitor of sex steroid formation is selected from the group consisting of aminoglutethimide, ketoconazole and pharmaceutical compositions thereof.
11. The method of claim 1 wherein said animal is treated with a therapeutically effective amount of an androgen.
12. The method of claim 11 wherein the androgen is medroxyprogesterone acetate ("MPA").
13. The method of claim 1 wherein said animal is treated with a therapeutically effective amount of an inhibitor of sex steroid formation.
14. The method of claim 13 where said inhibitor of sex steroid formation is N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\beta$ -dihydroxy estro-1',3',5'(10')trien-7' $\alpha$ -yl) undecanamide ("EM 139").
15. The method of claim 13 wherein said inhibitor of sex steroid formation is N-butyl, N-methyl-12,13-bis(4-hydroxyphenyl)-12-pentadecanamide ("EM 142").

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16. The method of claim 13 wherein said inhibitor of sex steroid formation is 6-methylenandrosta-1,4-diene-3,17-dione ("FCE 24304").
17. The method of claim 1 wherein said animal is treated with an androgen and an inhibitor of sex steroid formation.
18. The method of claim 17 wherein said inhibitor of sex steroid formation is selected from the group consisting of N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\beta$ -dihydroxy estra-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 139"), N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\alpha$ -dihydroxy estra-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 170"), N-butyl, N-methyl-11-(16' $\alpha$ -bromo-3',17' $\alpha$ -dihydroxy estra-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 171"), N-butyl, N-methyl-11-(3',17' $\beta$ -dihydroxy-16'-methylen estra-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 186"), N-butyl, N-methyl-11-(3'-hydroxy-16'-methylen estra-1',3',5'(10')-trien-17'-on-7' $\alpha$ -yl) undecanamide ("EM 175"), 17 $\beta$ -hydroxy-17 $\alpha$ -(12-iodo-dodecynyl)androst-4-en-3-one ("EM 150") and N-butyl, N-methyl-12,13-bis(4-hydroxyphenyl)-12-pentadecenamide ("EM 142").
19. The method of claim 1 wherein said androgen is 11 $\beta$ ,17 $\beta$ -dihydroxy-9 $\alpha$ -fluoro-17 $\alpha$ -methyl-androst-4-en-3-one ("Fluoxymesterone").
20. The method of claim 1 wherein said animal is treated with a therapeutically effective amount of a progestin.
21. The method of claim 3 wherein said inhibitor is administered at a daily parenteral dose of between 100 and 500 micrograms.

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22. The method of claim 20 wherein the progestin is 17,21-dimethyl-19-nor-4,9-pregnadiene-3,20-dione ("promegestone").
23. The method of claim 20 wherein the antiestrogen is N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\beta$ -dihydroxy estro-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 139").
24. The method of claim 20 wherein the antiestrogen is N-butyl, N-methyl-12,13-bis(4-hydroxyphenyl)-12-pentadecanamide ("EM 142").
25. The method of claim 20 wherein the antiestrogen is N-butyl, N-methyl-11-(16' $\alpha$ -bromo-3',17' $\alpha$ -dihydroxy estro-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 171").
26. The method of claim 20 wherein the antiestrogen is N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\alpha$ -dihydroxy estro-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 170").
27. The method of claim 20 wherein the antiestrogen is N-butyl, N-methyl-11-(16' $\alpha$ -iodo-3',17' $\beta$ -dihydroxy estro-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 156").
28. The method of claim 13 wherein the inhibitor of sex steroid formation is 4-hydroxyandrostenedione.
29. The method of claim 20 wherein the progestin is medroxyprogesterone acetate ("MPA").

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30. The method of claim 1 wherein said animal is treated with a therapeutically effective amount of a progestin and an inhibitor of sex steroid formation.
31. The method of claim 30 wherein said inhibitor of sex steroid formation comprises aminoglutethimide, ketoconazole or pharmaceutical compositions of either.
32. The method of claim 30 wherein the inhibitor of sex steroid formation is N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\beta$ -dihydroxyestra-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 139").
33. The method of claim 30 wherein the inhibitor of sex steroid formation is N-butyl, N-methyl-12,13-bis(4-hydroxyphenyl)-12-pentadecanamide ("EM 142").
34. The method of claim 30 wherein the inhibitor of sex steroid formation is 6-methylenandrosta-1,4-diene-3,17-dione ("FCE 24304").
35. The method of claim 30 wherein said progestin is 17,21-dimethyl-19-nor-4,9-pregnadiene-3,20-dione ("promegestone").
36. The method of claim 1 wherein said animal is treated with a therapeutically effective amount of both an androgen and a progestin.
37. The method of claim 36 wherein the androgen is medroxyprogesterone acetate ("MPA").

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38. The method of claim 36 wherein the progestin is 17,21-dimethyl-19-nor-4,9-pregnadiene-3,20-dione ("promegestone").
39. The method of claim 36 wherein the androgen is 11 $\beta$ ,17 $\beta$ -dihydroxy-9 $\alpha$ -fluoro-17 $\alpha$ -methyl-androst-4-en-3-one ("Fluoxymesterone").
40. The method of claim 17 wherein said inhibitor of sex steroid formation is aminoglutethimide, ketoconazole or pharmaceutical compositions of either.
41. The method of claim 17 wherein the androgen is medroxyprogesterone acetate ("MPA").
42. The method of claim 17 wherein the inhibitor of sex steroid formation is N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\beta$ -dihydroxyestra-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 139").
43. The method of claim 17 wherein the inhibitor of sex steroid formation is N-butyl, N-methyl-12,13-bis(4-hydroxyphenyl)-12-pentadecanamide ("EM 142").
44. The method of claim 17 wherein the inhibitor of sex steroid formation is 6-methylenandrosta-1,4-diene-3,17-dione ("FCE 24304").
45. The method of claim 17 wherein the inhibitor of sex steroid formation is 4-hydroxyandrostenedione.

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46. The method of claim 1 wherein said animal is treated with a therapeutically effective amount of an androgen, a progestin and an inhibitor of sex steroid formation.
47. The method of claim 46 wherein the androgen is medroxyprogesterone acetate ("MPA").
48. The method of claim 46 wherein the inhibitor of sex steroid formation is N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\beta$ -dihydroxyestra-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 139").
49. The method of claim 46 wherein the inhibitor of sex steroid formation is N-butyl, N-methyl-12,13-bis(4-hydroxyphenyl)-12-pentadecanamide ("EM 142").
50. The method of claim 46 wherein the inhibitor of sex steroid formation is 6-methylenandrosta-1,4-diene-3,17-dione ("FCE 24304").
51. The method of claim 46 wherein the progestin is 17,21-dimethyl-19-nor-4,9-pregnadiene-3,20-dione ("promegestone")
52. The method of claim 1 wherein said animal is treated with a therapeutically effective amount of a compound selected from the group consisting of an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.
53. The method of claim 11 wherein said animal is treated with a therapeutically effective amount of a compound selected from the group

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consisting of an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.

54. The method of claim 13 wherein said animal is treated with a therapeutically effective amount of a compound selected from the group consisting of an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.
55. The method of claim 17 wherein said animal is treated with a therapeutically effective amount of a compound selected from the group consisting of an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.
56. The method of claim 20 wherein said animal is treated with a therapeutically effective amount of a compound selected from the group consisting of an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.
57. The method of claim 30 wherein said animal is treated with a therapeutically effective amount of a compound selected from the group consisting of an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.
58. The method of claim 36 wherein said animal is treated with a therapeutically effective amount of a compound selected from the group consisting of an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.

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59. The method of claim 46 wherein said animal is treated with a therapeutically effective amount of a compound selected from the group consisting of an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.
60. The method of claim 52 wherein the inhibitor of prolactin secretion is bromocriptine.
61. The method of claim 52 wherein the inhibitor of growth hormone secretion is Sandostatin.
62. A kit for treatment of breast or endometrial cancer, said kit including a pharmaceutical composition comprising an antiestrogen and at least one pharmaceutical composition selected from the group consisting of a pharmaceutical composition comprising a progestin, a pharmaceutical composition comprising an inhibitor of sex steroid formation, a pharmaceutical composition comprising an inhibitor of prolactin secretion, a pharmaceutical composition comprising an inhibitor of ACTH secretion and a pharmaceutical composition comprising an inhibitor of growth hormone secretion.
63. The kit of claim 62 further containing a pharmaceutical composition comprising an androgen.
64. The kit of claim 62 further comprising an ovarian secretion inhibitor.

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65. The kit of claim 63 further comprising an ovarian secretion inhibitor.
66. The kit of claim 62 wherein said kit includes a pharmaceutical composition comprising a progestin.
67. The kit of claim 62 wherein said kit includes a pharmaceutical composition comprising an inhibitor of sex steroid formation.
68. The kit of claim 62 wherein said kit includes a pharmaceutical composition comprising an inhibitor of prolactin secretion.
69. The kit of claim 62 wherein said kit includes a pharmaceutical composition comprising an inhibitor of ACTH secretion.
70. The kit of claim 63 wherein said kit includes a pharmaceutical composition comprising an inhibitor of sex steroid formation.
71. The kit of claim 63 wherein said kit includes a pharmaceutical composition comprising an inhibitor of ACTH secretion.
72. The kit of claim 63 wherein said kit includes a pharmaceutical composition comprising a progestin.
73. The kit of claim 63 wherein said kit includes a pharmaceutical composition comprising a progestin and an inhibitor of sex steroid formation.

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74. The kit of claim 64 wherein said ovarian secretion inhibitor comprises an LHRH agonist or an LHRH antagonist.
75. The kit of claim 65 wherein said ovarian secretion inhibitor comprises an LHRH agonist or an LHRH antagonist.
76. The kit of claim 62 wherein said antiestrogen is capable of acting as an inhibitor of sex steroid formation.
77. The kit of claim 67 wherein said antiestrogen composition and said inhibitor of sex steroid formation composition are the same or comprise the same active ingredient.
78. The kit of claim 63 wherein the pharmaceutical compositions of the androgen and the antiestrogen are each oral compositions.
79. A method of treating breast or endometrial cancer in a warm-blooded animal wherein said method comprises administering to said animal therapeutically effective amounts of an antiestrogen and at least one compound selected from the group consisting of a progestin, an inhibitor of sex steroid formation, an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.
80. The method of claim 79 wherein the antiestrogen is selected from the group consisting of (Z)-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine ("Tamoxifen"), N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\beta$ -dihydroxy estra-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide

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("EM 139"), N-butyl, N-methyl-12,13-bis(4-hydroxyphenyl)-12-pentadecanamide ("EM 142"), N-butyl, N-methyl-11-(16' $\alpha$ -iodo-3',17' $\beta$ -dihydroxy estro-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 156"), N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\alpha$ -dihydroxy estro-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 170"), N-butyl, N-methyl-11-(16' $\alpha$ -bromo-3',17' $\alpha$ -dihydroxy estro-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 171").

81. The method of claim 79 wherein said animal is treated with a therapeutically effective amount of an inhibitor of sex steroid formation.
82. The method of claim 81 wherein said inhibitor of sex steroid formation is selected from the group consisting of N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\beta$ -dihydroxy estro-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 139"), N-butyl, N-methyl-11-(16' $\alpha$ -chloro-3',17' $\alpha$ -dihydroxy estro-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 170"), N-butyl, N-methyl-11-(16' $\alpha$ -bromo-3',17' $\alpha$ -dihydroxy estro-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 171"), N-butyl, N-methyl-11-(3',17' $\beta$ -dihydroxy-16'-methylen estro-1',3',5'(10')-trien-7' $\alpha$ -yl) undecanamide ("EM 186"), N-butyl, N-methyl-11-(3'-hydroxy-16'-methylen estro-1',3',5'(10')-trien-17'-on-7' $\alpha$ -yl) undecanamide ("EM 175"), 17 $\beta$ -hydroxy-17 $\alpha$ -(12-iodo-dodecynyl)andro-4-en-3-one ("EM 150") and N-butyl, N-methyl-12,13-bis(4-hydroxyphenyl)-12-pentadecanamide ("EM 142"), 6-methylenandrosta-1,4-diene-3,17-dione ("FCE 24304") and 4-hydroxyandrostenedione.

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83. The method of claim 79 wherein said animal is treated with a therapeutically effective amount of an androgen.
84. The method of claim 83 wherein said androgen is selected from the group consisting of medroxyprogesterone acetate (MPA) and Fluoxymesterone.
85. The method of claim 79 wherein said animal is treated with a therapeutically effective amount of a progestin.
86. The method of claim 85 wherein the progestin is 17,21-dimethyl-19-nor-4,9-pregnadiene-3,20-dione ("promegestone") or medroxyprogesterone acetate (MPA).
87. The method of claim 79 wherein said animal is treated with a therapeutically effective amount of a progestin and an inhibitor of sex steroid formation.
88. The method of claim 79 wherein said animal is treated with a therapeutically effective amount of both an androgen and a progestin.
89. The method of claim 79 wherein said animal is treated with a therapeutically effective amount of an androgen, a progestin and an inhibitor of sex steroid formation.

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90. The method of claim 79 wherein said animal is treated with a therapeutically effective amount of a compound selected from the group consisting of an inhibitor of prolactin secretion, an inhibitor of growth hormone secretion and an inhibitor of ACTH secretion.
91. A therapeutic pharmaceutical composition for treatment of breast or endometrial cancer, said pharmaceutical composition comprising a therapeutically effective amount of an antiestrogen and of at least one pharmaceutical compound selected from the group consisting of a progestin, an inhibitor of sex steroid formation, an inhibitor of prolactin secretion, an inhibitor of ACTH secretion and an inhibitor of growth hormone secretion.
92. The pharmaceutical composition of claim 91 wherein said composition further comprises an androgen.
93. The pharmaceutical composition of claim 91 wherein said composition further comprises an ovarian secretion inhibitor.
94. The pharmaceutical composition of claim 92 wherein said composition further comprises an ovarian secretion inhibitor.
95. The pharmaceutical composition of claim 91 wherein said composition further comprises a progestin.
96. The pharmaceutical composition of claim 91 wherein said composition further comprises an inhibitor of sex steroid formation.

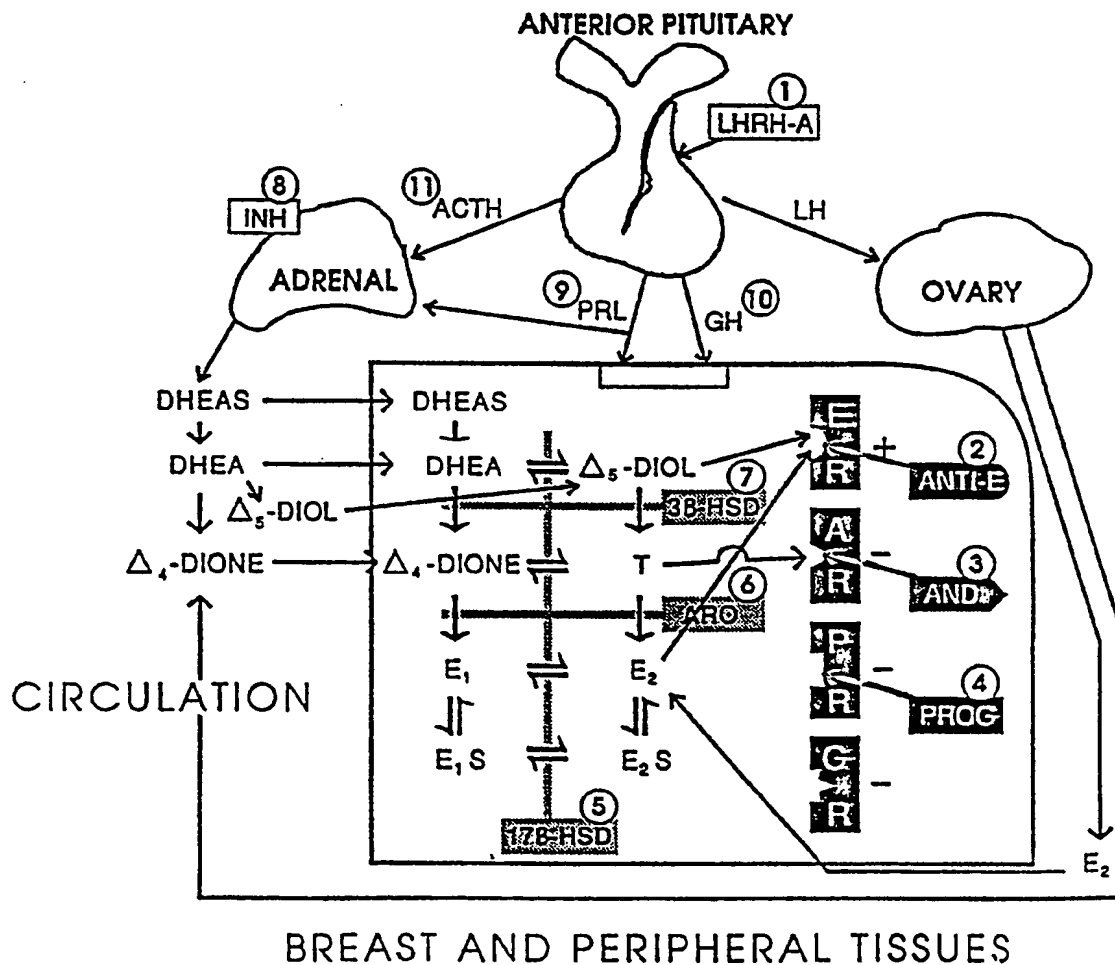
**SUBSTITUTE SHEET**

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97. The pharmaceutical composition of claim 91 wherein said composition further comprises an inhibitor of prolactin secretion.
98. The pharmaceutical composition of claim 91 wherein said composition further comprises an inhibitor of ACTH secretion.
99. The pharmaceutical composition of claim 92 wherein said composition further comprises an inhibitor of sex steroid formation.
100. The pharmaceutical composition of claim 92 wherein said composition further comprises an inhibitor of ACTH secretion.
101. The pharmaceutical composition of claim 92 wherein said composition further comprises a progestin.
102. The pharmaceutical composition of claim 92 wherein said composition further comprises a progestin and an inhibitor of sex steroid formation.
103. The pharmaceutical composition of claim 93 wherein said ovarian secretion inhibitor comprises an LHRH agonist or an LHRH antagonist.
104. The pharmaceutical composition of claim 91 wherein said antiestrogen is capable of acting as an inhibitor of sex steroid formation.
105. The pharmaceutical composition of claim 91 wherein a single compound provides both antiestrogenic activity and inhibition of sex steroid formation.

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FIG. 1



# INTERNATIONAL SEARCH REPORT

International Application No **PCT/CA 90/00076**

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>4</sup> According to International Patent Classification (IPC) or to both National Classification and IPC IPC <sup>5</sup> : A 61 K 45/06, 37/43, 31/56, 31/57, 31/575, // (A 61 K 37/43, 31:135), (A 61 K 31/575, 31:57, 31:56, 31:135), ./.											
<b>II. FIELDS SEARCHED</b> <div style="text-align: center;">Minimum Documentation Searched <sup>7</sup></div> <table style="width: 100%; border: none;"> <tr> <td style="width: 25%; border: none;">Classification System</td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none; vertical-align: top;">IPC<sup>5</sup></td> <td style="border: none; vertical-align: top;">A 61 K 31</td> </tr> </table> <div style="text-align: center; padding-top: 10px;">Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched <sup>8</sup></div>			Classification System	Classification Symbols	IPC <sup>5</sup>	A 61 K 31					
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# INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 90/00076<sup>-2-</sup>

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, " with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	Dialog, Cancerlit abstr. 88744134, M. Resnicoff et al.: "Combination of a somatostatin analogue, sandostatin (SMS), Tamoxifen (T) and estradiol (E) induces an important lytic effect on estrogen receptor (ER)-positive breast cancer cell lines", see abstract 0621930 & Proc. Annu. Meet Am. Assoc. Cancer Res, 29:A930, 1988 --	62,91
X	EP, A, 0151326 (MAUVAIS-JARVIS) 14 August 1985 . see claim 3 --	62,91,66,95
X	Chemical Abstracts, vol. 109, 1988, (Columbus, Ohio, US), S.E. Grenman et al.: "In vitro growth regulation of endometrial carcinoma cells by tamoxifen and medroxypro- gesterone acetate", see page 92, abstract 32346c, & Gynecol. Oncol. 1988, 30(2), 239-50 --	62,66,91,95
X	Chemical Abstracts, vol. 108, 1988, (Columbus, Ohio, US), H. Ishikawa et al.: "Combined therapies with medroxyprogesterone acetate (MPA) for DMBA-induced rat mammary tumor and advanced human breast cancer", see page 90, abstract 198573d, & Hormon to Rinsho 1987, 35(12), 1359-66 --	62,66,91,95
X	Chemical Abstracts, vol. 104, 1986, (Columbus, Ohio, US), T. Tominaga et al.: "Effective sequential administration of tamoxifen and medroxyprogesterone acetate for 7,12-dimethylbenz(a)-anthracene- induced rat mammary tumors in relation to hormone receptors", see page 93, abstract 62317h, & Jpn. J. Cancer Res. (GANN) 1985, 76(11), 1120-5 --	62,66,91,95

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X	Chemical Abstracts, vol. 100, 1984, (Columbus, Ohio, US), P. Robel et al.: "Female sex steroid receptors in postmenopausal endometrial carcinoma. Biochemical responses to antiestrogen and progestin", see page 83, abstract 203835g, & Prog. Clin. Biol. Res. 1984, 142(Horm. Cancer), 167-79	62,66,91,95
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## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>1</sup>

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers XX because they relate to subject matter not required to be searched by this Authority, namely:

xx Claims 1-61, 19-90

Pls see Rule 39.1 (iv) - PCT:

Method for treatment of the human or animal body by surgery or therapy as well as diagnostic mehtods.

2. ☐ Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>2</sup>

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

CA 9000076  
SA 35477

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on 09/07/90  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0151326	14-08-85	FR-A, B 2558373	26-07-85
		WO-A- 8503228	01-08-85
		EP-A- 0169214	29-01-86
		JP-T- 61500914	08-05-86
		US-A- 4919937	24-04-90
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82